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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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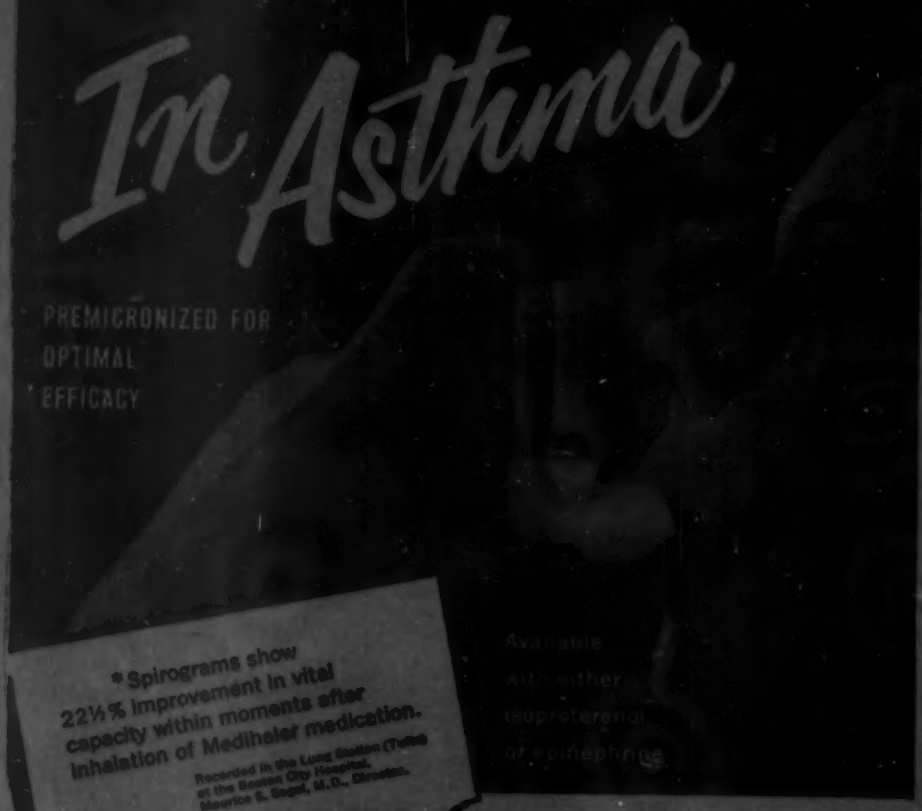

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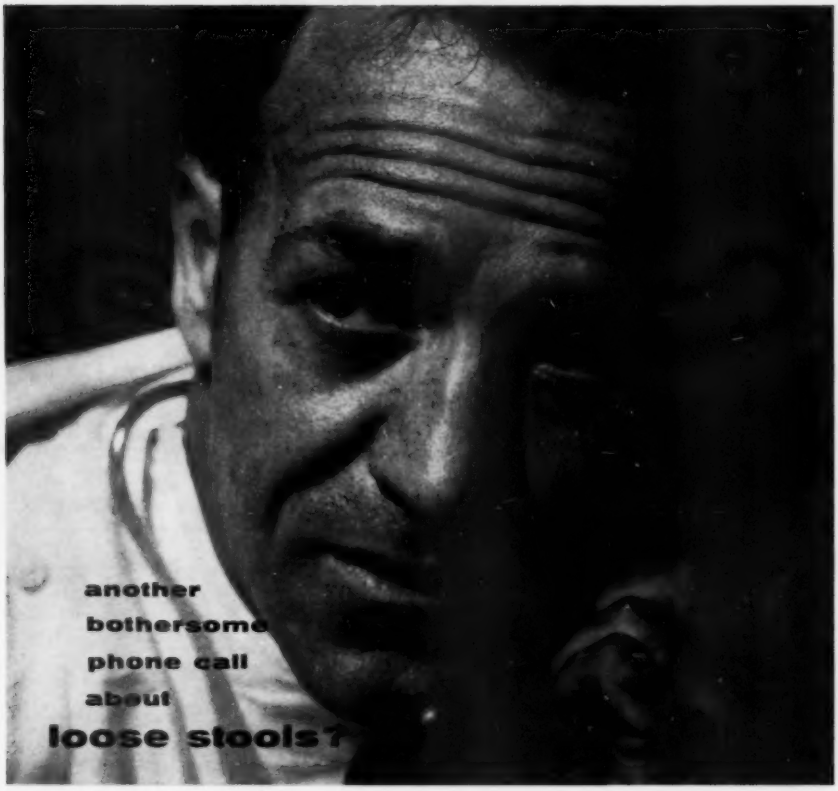

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2 mo.	27	1
3 mo.	12	1
4 mo.	10	1
5 mo.	14	0
6 mo.	8	0
7 mo.	19	0
8 mo.	11	0
9 mo.	10	0
10 mo.	8	0
11 mo.	11	0
12 mo.	10	0
	190	3 (1.6%)

†Exclusive of infants admitted with infectious diarrhea.

1. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585-592 (Nov.) 1951.
2. Henrickson, W. E.: GP 8:51-56 (Oct.) 1953.

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References: 1. Crunk, G. A.; Naumann, D. E., and Casson, K.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia Inc. 1958, p. 397 • 2. Newcomer, V. D.; Wright, E. T., and Sternberg, T. H.: Antibiotics Annual 1954-1955, New York, Medical Encyclopedia Inc., 1955, p. 686.

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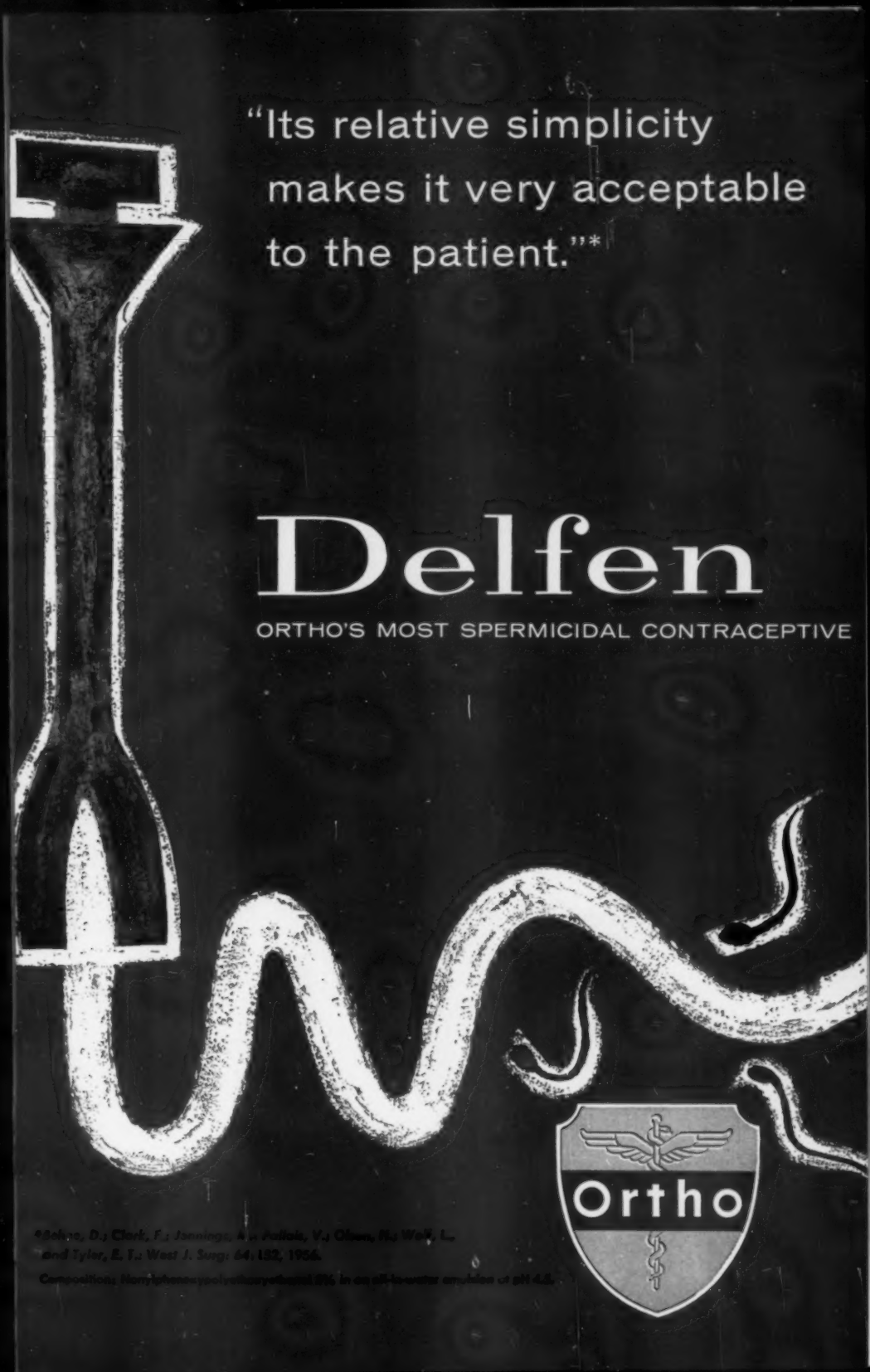
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*Carter, S.: *M. Clin. North America*: 315 (March) 1953.

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1. McClendon, S.J.: Arch. Pediat. 75:101 (March) 1958.

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J.A.M.A. 169:257 (January 17) 1959.

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"As with other glucocorticoids, the long-term administration of triamcinolone results in definite catabolic effects, as indicated by impairment of carbohydrate utilization and negative protein and calcium balance. This catabolic effect, coupled with a lack of appetite stimulation which is apparently peculiar to triamcinolone, may produce weight loss that might be undesirable in some patients treated for long periods of time."

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"Triamcinolone appears to compare favorably with other steroids for use in those situations in which edema and sodium retention have been complicating problems."

"It [triamcinolone] may also be the steroid of choice for patients in whom psychic stimulation, euphoria, voracious appetite, and weight gain should be avoided."

"...the drug [triamcinolone] does produce the other side effects and untoward reactions common to the glucocorticoids. At therapeutically equivalent doses, the frequency and severity of clinical manifestations of hyperadrenalism — rounding of the face, fat deposition, and hirsutism — are essentially the same. Likewise, there is little indication that the relative incidence of osteoporosis is materially decreased after the long-term use of the drug."

"Triamcinolone apparently does not cause the euphoria sometimes seen with other steroids, and the occurrence of mental depressions is uncommon."

"Current evidence suggests that the drug [triamcinolone] may not produce as high an incidence of peptic ulcer as do other steroids."

"Cutaneous erythema seems to be a side effect peculiar to triamcinolone."

"The usual contraindications and precautions of glucocorticoid therapy should be followed in the use of triamcinolone, keeping in mind that prolonged therapy with this drug will suppress the function of the patient's own adrenals by interfering with the pituitary-adrenal axis."

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 35, NO. 5 MAY 1959

PRIMARY CARCINOMA OF THE LIVER*

Thirteenth James Ewing Memorial Lecture

CHARLES BERMAN**

I WISH to thank Doctor L'Esperance and the James Ewing Memorial Committee for inviting me to deliver this, the Thirteenth James Ewing Memorial Lecture. I appreciate this honor all the more since I realize that I am perhaps the first colleague from outside the United States who has been afforded the privilege of paying tribute to the memory of one of America's greatest sons. For James Ewing's fame as a physician transcends all national boundaries and barriers: his outstanding contributions to cancer pathology were as well-known to his colleagues throughout the world in his own lifetime as they are to this day.

From my earliest student days I have admired his monumental work, "Neoplastic Diseases", for its erudition, lofty scholarship, and above all, for its clinical approach to a problem in pathology that is still so baffling. It was to this great work, therefore, that I turned at the beginning of my own researches into primary liver cancer.

In dedicating his life to the understanding of cancer, James Ewing helped found the great American Cancer Society and the world-famous

* Given at the Stated Meeting of The New York Academy of Medicine, May 1, 1958.

** M. R. C. P. (London); Visiting Associate, Sloan-Kettering Institute for Cancer Research; Special Fellow in Surgery, Memorial Center for Cancer and Allied Diseases, New York, N. Y.; Senior Medical Officer, Consolidated Main Reef Mines and Estate, Ltd., Maraisburg, Transvaal, South Africa.

New York Memorial Center for Cancer and Allied Diseases, and these will remain fitting and constant reminders of James Ewing's endeavours to ameliorate one of the greatest causes of human suffering.

Primary carcinoma of the liver is a remarkable form of malignancy. It is remarkable not only because of its demographic and geographic distribution, its early age incidence in African and some Oriental races, but also because of the ease with which it can be induced in experimental animals by specific environmental factors.

Tonight's lecture is based mainly on my book[1] and on my recent review of the subject[2]. It will be considered under four headings: (I) Incidence (II) Pathology (III) Clinical Manifestations (IV) Etiology.

I. Incidence

From a survey of the World's available postmortem statistics, it would seem that the incidence of primary liver cancer varies strikingly among the different races of mankind. Of rare occurrence among the peoples of Western Europe and America, it is by contrast remarkably common among the aboriginal inhabitants of Africa and certain parts of Asia.

Geographically, the areas of known or suspected high prevalence of the disease extend from the west African coast and central Africa south of the Sahara Desert, along eastern and southeastern portions of Africa and across eastern and southeastern Asia, including particularly Indonesia, the Philippines, China and Japan.

Western Races. Primary liver cancer is rare among all Western people irrespective of whether they live in Europe, America, Africa, Asia or elsewhere. The postmortem rate averaged 0.14 per cent in Europe and 0.27 per cent in the United States of America, and the relative frequency of this tumor among all malignancies was 1.2 per cent and 2.5 per cent respectively.

Oriental Races. Among Oriental people, on the other hand, the autopsy rate was approximately 0.8 per cent, and the relative frequency of primary liver cancer to all other cancers was almost 14 per cent. A very high incidence of the disease was noted in Indonesians (41.6 per cent of all cancers) followed by Chinese (33 per cent) and Filipinos (22 per cent). Relatively high frequencies have also been recorded in certain parts of India and in Japan.

African Races. The highest frequency of the disease, however, has been observed in Africa. Thus, primary liver cancer is extraordinarily common among the Bantu and other indigenous people inhabiting the vast territorial regions south of the Sahara Desert. According to recorded statistics, the postmortem rate varied between 0.7 per cent in Kenya and 2.4 per cent in South Africa (average 1.1 per cent), and the relative frequency of primary liver cancer to all carcinomata ranged between 17 per cent and 53 per cent.

In many parts of Africa, moreover, primary liver cancer has been found to be the most frequent form of internal cancer, especially in relatively young adult males.

In Le Dantec Hospital at Dakar, French West Africa, for example, 60 cases (representing 75 per cent of all cancers) are treated annually[3], and approximately 100 new primary liver cancers are sectioned every year at the Pasteur Institute of that city[4]. At the great Memorial Center of New York, on the other hand, not more than six cases are treated in any year[5].

For French West Africa as a whole during the 16-year period 1940-1955, 1455 cases of primary liver cancer were documented[6]. These included 1227 cases in males and 228 cases in females, among whom primary liver cancer averaged 48.3 per cent and 14.7 per cent of all cancers, respectively, with annual ranges of 16 per cent to 65 per cent in males and 5 per cent to 18 per cent in females. These remarkable statistics from a single geographical region recorded over a relatively short period of time are in striking contrast with the total 1391 cases of primary liver cancer which up to 1950 Carnahan[7] was able to compile from the entire world's literature.

In South Africa, primary liver cancer is very prevalent among the migratory Bantu laborers of the gold mines, who are a specially selected and fit group of young men recruited from various tropical and subtropical regions of central and southern Africa. This tumor was responsible for 670 out of 772 cases (87 per cent) of all carcinomata. It is significant that the liver cancers were found almost six times more frequently in Bantu mine workers hailing from Portuguese East Africa than in those from South Africa.

Primary Liver Cancer in Animals and Birds. It is appropriate to mention that primary liver cancer is not unusual in lower animal life. Spontaneous liver cancers have been described in cattle and in most

domestic animals, including dogs, ducks, sheep, cats, horses, pigs, fowl, as well as in a few wild mammals and in birds.

Sex and Age Incidence. Primary liver cancer occurs predominantly in males, although there seems to be an enhanced frequency of the disease in female Africans when compared with those of other races.

Among Africans[1-3] and Indonesians[8, 9], the disease is pre-eminently one of youth, occurring mainly under the age of 40 years and very often before the age of 20 or 30 years.

In other races it is commonest at or after middle age, and is rare before the age of 40. No age, however, is exempt; for the tumor occurs also in the very old and has been discovered in children of all ages[10]. The youngest African case that I have seen was that of a boy aged nine years.

II. Pathology

Gross Pathology

The liver in primary hepatic cancer is always increased in size and weight. In my own series of cases, the maximum weight observed in any individual case was 7,100 gm., the minimum 1,900 gm., and the average, 3,870 gm. (The normal liver weight is 1,500 gm.)

For practical and descriptive purposes, primary liver cancer can be divided into two macroscopic groups: *nodular* carcinoma, a tumor formed of numerous discrete nodules of varying sizes, and *massive* cancer, consisting mainly of a single large dense mass. Both forms involve the right more than the left lobe of the liver, and the intervening liver tissue is usually the site of varying degrees of fibrosis or cirrhosis.

Nodular Cancer. The liver is large, hard, scarred, deformed and studded with closely grouped or irregular nodular masses. On section, much of its substance is seen to be replaced by firm, scattered or closely grouped nodules mostly white to grey in color, although they may also be reddish or soft and friable, when they are often found occupying portal or hepatic veins as tumor emboli.

Massive Cancer. The enlarged liver is distorted by a uniform smooth swelling with occasional secondary irregularities in its vicinity. On section, the tumor mass is found occupying practically the whole right lobe to which it is confined, but there may be additional smaller growths localised especially at the periphery. It may be soft, cystic, hemorrhagic or cartilagenous and its color may vary from white to grey.

A sharp demarcation between the two macroscopic groups is often not possible, for many tumors originally "nodular" in character tend to transform into "massive" cancers. It is then that the tumor may be so extensive that scarcely any normal liver remains.

HISTOPATHOLOGY

Primary liver cancer occurs in two forms, hepatocellular and cholangiocellular cancer. It is generally assumed, but not positively proved, that hepatocellular cancer originates from the cells of the liver lobules, and cholangiocellular cancer from the cell of the intrahepatic bile ducts. Mixed or hepatobiliary cancer may also occur.

Hepatocellular Cancer. This, the most frequent form of primary liver cancer, has a characteristic structure. The tumor cells are usually larger than normal liver cells, which they resemble: they are polygonal in shape with distinct borders, and when stained with hematoxylin and eosin show an abundant eosinophilic or moderately basophilic granular cytoplasm. The nuclei are bizarre, reach extraordinary dimensions and frequently occupy almost the whole cell: they are oval to spherical in shape, are markedly hyperchromatic, and although usually single, some cells may have two or more such nuclei containing purple-staining nucleoli. Mitotic figures in various phases are frequent, and giant cells containing single or multiple nuclei are often observed.

The tumor cells are characteristically arranged as compact trabeculae varying from 2 to 30 cells in thickness and devoid of intercellular stroma. These cell columns either anastomose with one another or are arranged as long parallel columns, which terminate freely as blunt, rounded extremities. Their margins are bordered by a single layer of endothelium resembling Kupffer cells, which adhere closely to the peripheral tumor cells, forming in this way a pronounced vascular stroma containing reticulum: numerous vascular spaces between adjacent cancer columns are thus formed varying in width—some containing much blood. Bile pigment is often seen in the tumor cords. In the more anaplastic tumors, however, this trabecular arrangement is less evident or even absent. The rest of the liver is usually the seat of cirrhosis.

Apart from fatty and scirrhous changes in the tumor cells, necrosis often occurs, affecting particularly the most central parts of the tumor columns. These necrotic areas are liable to hemorrhage, and if such

tumor nodules are superficially placed, alarming intraperitoneal hemorrhage may occur, often with rapidly fatal results.

Cholangiocellular Cancer. Cholangiocellular carcinoma occurs far less frequently than hepatocellular cancer. It is characterised by a glandular structure and an alveolar pattern of arrangement.

The tumor cells are columnar to cuboidal in shape and show some resemblance to bile-duct epithelium. The cytoplasm is nongranular and faintly acidophilic or basophilic. Their prominent nuclei are round, oval or spindleshaped, are proximally situated, and at times extend along the whole axis of the cell: they are particularly hyperchromatic, stain intensely with hematoxylin and contain single large nucleoli. Mitotic figures are frequent, but giant cells are rare.

In cholangiocellular cancer the cells are arranged in alveoli of varying shapes and sizes – a characteristic which distinguishes them from the solid trabecular formation of the hepatocellular cancers. The tubules are irregular or multiloculated cystic spaces lying in a pronounced fibrous tissue stroma, or they may be separated from each other by open spaces. The lumina of the tubules may be clear or contain degenerating tumor cells and mucus. Reticulum is scanty or absent.

METASTASES

Primary liver cancer possesses vigorous metastatic powers and dispersal may often be widespread.

a) *Intrahepatic Metastases.* Metastases within the liver commence at an early stage when individual tumor cells spread along the sinusoids to become organized as proliferating tumor nodules; or they characteristically penetrate the wall of a portal vein, which then becomes filled with proliferating groups of tumor cells that grow steadily, until the whole vessel and its branches (best seen in the vessels of the cirrhotic tracts) become occluded by a continuous tumor thrombus. With the invasion of the portal system, dissemination to other parts of the liver readily occurs. In this way, a single primary focus may give rise to widespread intrahepatic metastases.

b) *Extrahepatic Metastases.* Secondary deposits outside the liver occur in 50 to 75 per cent of cases. They are often multiple and may arise at a stage when the primary hepatic growth is still symptomless. Extrahepatic metastases begin with the invasion of the hepatic or portal veins. Dislodged tumor cells and cancerous thrombi reach the inferior

vena cava (which often escapes infiltration) and are conveyed via the heart to the terminal arterioles in the lungs. Here they proliferate, invade the surrounding lung tissue, and by penetrating the pulmonary veins become the source of systemic dissemination, although in exceptional cases the tumor cells pass directly into the general circulation without involving the lungs. The lungs are the most common sites for metastases. To a lesser extent, metastatic spread occurs also by way of the lymphatic vessels. In this way metastases may be found in any part of the body.

There is a close resemblance in histological structure between the metastases and the parent hepatocellular and cholangiocellular liver tumors. The metastatic deposits may become highly organized and even show unmistakable bile production in such distant situations as the lungs, bone, etc.

III. Clinical Manifestations

The clinical course of primary liver cancer is not constant. Symptomatology is dependent upon the degree of associated cirrhosis, the rate of tumor growth, upon complications, and upon the development of metastases.

Mode of Onset

The disease usually makes steady, silent progress over an indefinite period of time and the patient is generally unaware of his condition until the malignant liver has reached alarming proportions.

Owing to the insidious nature of the condition, the disease:

1. May be ushered in with dramatic suddenness as an acute abdominal catastrophe following rupture of a necrotic nodule or erosion of a blood vessel on the free surface of the liver. This happens in about 8 per cent of cases.

2. May first manifest itself equally abruptly as a rapidly growing and necrotic tender liver accompanied by fever, and these symptoms may simulate an amebic abscess, from which it may be difficult to distinguish it — 5 per cent of cases.

3. Again, also in about 5 per cent of cases, symptoms due to extrahepatic metastases in remote organs or parts may be the first to direct attention to what may prove to be a symptomless primary liver cancer—e.g., tumors of the skull, spine, ribs, clavicle, etc.

4. The liver tumor, on the other hand, may remain latent until discovered accidentally during a clinical "work up", or even only at autopsy: this occurs in about 16 per cent of cases.

SYMPTOMATOLOGY

In established liver cancer, the prodromal signs are usually vague and indefinite and are most often attributed to gastro-intestinal disturbances. When present, they may include lack of appetite, nausea, vomiting, diarrhoea, abdominal pressure and a sense of fullness in the upper abdomen after meals.

The most constant symptoms are: progressive muscular weakness (86 per cent of cases); loss of weight and emaciation (83 per cent of cases); and abdominal pain of a dull character localized to the right hypochondrium and unrelated to food (90 per cent of cases).

The liver is always enlarged, often to a remarkable degree. Its surface is usually nodular and tender; and its firm lower outline may be visible as well as palpable, and may extend upwards into the thorax and downwards to the level of the umbilicus or even lower.

Jaundice develops at a late stage of the disease in approximately half the cases; as also does ascites, with straw-colored or blood-stained fluid. Secondary anemia is almost invariably present. Signs pointing to portal hypertension, including dilatation of the superficial abdominal veins and edema of the lower extremities, occur in approximately one third of cases. Occasionally there is hematemesis from rupture of esophageal or gastric varices, and this may terminate fatally. The temperature is normal or moderately elevated, but the pulse may be raised even in cases without fever.

DIAGNOSIS

Regarding a patient with an enlarged liver in whom cancer is suspected, the following questions must be answered:—

1. Is the tumor part of the liver, or is it part of a neighbouring organ, e.g., stomach, kidney?

2. If the organ involved is considered to be the liver, is the enlargement due to local or to general causes?

3. If malignancy is suspected, does the neoplasm arise primarily in the liver or is it a metastasis secondary to cancer in a remote organ, e.g., stomach, colon, rectum, etc.?

Certain diagnosis of primary liver cancer is made only after consideration of the clinical manifestations and evaluation of the tumor material obtained by biopsy or at operation.

Aids to the Diagnosis of Primary Liver Cancer

1. *Liver puncture biopsy* is invaluable for determining the nature of obscure liver enlargements. The procedure, however, is not without danger, for hemorrhage or biliary peritonitis may occur. The tumor itself, moreover, may be missed.

2. *Liver function tests* are useful only insofar as they indicate the presence of general diffuse liver damage. They are not capable of pointing to the actual cause of the disease[11], as they cannot differentiate primary from secondary liver cancer or from cirrhosis.

3. *Roentgenography* will define the shape and size of the liver, elevation of the diaphragm and restriction of its movements, as well as localisation of pulmonary metastases. Examination by barium swallow for esophageal varices secondary to the associated cirrhosis, and evidence pointing to displacement and distortion of the stomach and duodenum by the liver tumor are also helpful in making the diagnosis[12].

4. *Portal-splenic venography*: Injection of radiopaque "Diodone" percutaneously into the spleen, followed by immediate roentgenography of the liver, will show the portal vein and its branches clearly outlined in unaffected portions of the liver, but in cancerous areas these are distorted or devoid of contrast medium[13].

5. *Abdominal aortography*: Injection into the aorta of a contrast medium, e.g., "Urokon", followed by rapid roentgenography, will show primary and secondary liver cancers as areas of diminished vascular density[14, 15].

PROGNOSIS

The outlook of primary liver cancer is hopeless, for it is generally a rapidly fatal disease. In my own series of cases, the duration of the disease was never longer than four months from the first appearance of symptoms, and the stay in hospital varied from one to 81 days, the average being 21 days.

TREATMENT

1. *Medical Treatment.* Owing to the hopelessness of the disease, medical treatment is essentially palliative and is directed towards the

relief of pain and discomfort. Sedatives are always required in increasingly frequent doses. In the terminal stages of the disease the condition can be ameliorated by means of steroids; and in the treatment of ammonia toxicity, which often occurs, the administration of glutamic acid derivatives, antibiotics and colonic irrigations may be helpful.

2. *Chemotherapy*. Chemotherapeutic agents have not proved beneficial as yet for the treatment of the disease. Nitrogen mustard (HN_2) and allied compounds have been tried to control diffuse and inoperable cancers of the liver, but the results have not been encouraging[16].

3. *Radiotherapy*. It is possible that radiotherapy may be of value in treating early stages of the disease but more information is necessary. Recent observations have indicated that the liver appears to tolerate large doses of radiation delivered by super-voltage machines and that the lives of patients with liver cancer are somewhat prolonged thereby, although the effect seems temporary[17-19].

4. *Radioactive Isotopes*. Little is known about the effects of isotopes on primary liver cancer. At the New York Memorial Center for Cancer and Allied Diseases, however, radioactive iridium implanted by means of long needles directly into extensive and inoperable liver cancer is currently being used, and the results are awaited with interest.

5. *Surgical Treatment*. The experience of treating primary liver cancer by surgical excision has generally been disappointing, mainly because of the onset of recurrences, the presence of latent intrahepatic or extrahepatic metastases at the time of operation, and also because of the associated cirrhosis in the unaffected portions of the liver.

Surgical treatment must be considered if at laparotomy the tumor is found to be small, circumscribed, solitary, and particularly if it involves only the left lobe of the liver. The tumor is then excised by partial lobectomy, due care being taken to control hemorrhage, which may be alarming. Removal of the more frequently involved right lobe of the liver by total right hepatic lobectomy has been regarded in the past as too hazardous an undertaking. This attitude, however, has now changed. Thanks to the current advances in surgical and anesthetic techniques, a number of successful total right hepatic lobectomies for primary liver carcinoma have been carried out[20-23].

The essential requirements for total right hepatic lobectomy include:

a) *Choice of case*: The right lobe of the liver alone is involved by the tumor, there being in the opinion of the operator no intrahepatic

metastases to the left lobe, no extrahepatic metastases, and minimal cirrhosis.

b) *Absolute control of hemorrhage*: To effect this the surgical approach should be wide, preferably by means of an abdominothoracic incision. Before any attempt is made to remove the right lobe of the liver, it is essential to isolate and ligate the right hepatic artery, the right bile duct, and the right hepatic veins. It is important that the operation sites should be adequately drained.

IV. Etiology

The true cause of primary liver cancer, like that of cancer in general, is unknown. From experimental and clinical evidence, however, it is becoming apparent that environmental factors may play a vital role in the etiology.

Induced Liver Cancer in Experimental Animals. Few fields of experimental cancer research have yielded more striking results than the production of primary liver cancer in laboratory animals with compounds of known chemical composition, which, moreover, are specifically carcinogenic for the liver. Outstanding examples of these are the azo-compounds, o-aminoazotoluene[24] and p-dimethylaminoazobenzene ("butter yellow")[25], the essential effects of which are fatty and destructive changes in the liver parenchyma followed by cirrhosis, progressive hyperplasia of the regenerating liver and bile duct cells, leading ultimately to hepatocellular, cholangiocellular, or "mixed" cancer.

The induced liver cancers are easily transplantable and production of the tumors can be modified by diet[26]. A low protein – high fat or rice diet, or one deficient in methionine, riboflavin, or cystine increases the incidence of the tumor, whereas a high protein diet or one containing methionine, vitamin B complex or yeast has the opposite effect. It is interesting to note in this connection that factors which modify the incidence of experimental liver cancer have the same effects in experimental nutritional liver cirrhosis.

Cancer development, however, is not necessarily connected with the seriousness of the existing liver cirrhosis, and although cirrhosis usually precedes a liver tumor, it is not necessarily a predecessor of the lesion. Nevertheless, all are agreed that the liver tumors appear earlier in rats fed on a cirrhosis-producing diet.

Sex hormones seem to influence the development of experimental

liver tumors: androgens stimulate, and estrogens appear to inhibit carcinogenesis. In spontaneous mouse liver tumors and in rat liver tumors induced with "butter yellow", the incidence is much higher in males, but with castration is lowered to approximately the incidence level in females.

Other carcinogenic compounds used to induce liver tumors include: dibenzcarbazole, methylcholanthrene, acetylaminofluorene (which induces at the same time tumors of the bladder, renal pelvis, pancreas and lungs), selenium, carbon tetrachloride, ethylurethane, tannic acid and senecio alkaloids.

Carcinogenic factors from Human Livers, Tissues and Excretions. The discovery that the carcinogenic hydrocarbon, methylcholanthrene, is chemically related to naturally occurring biological products, e.g., bile acids and sterols, has given rise to the speculation whether carcinogenic compounds may actually be formed in the human body.

Investigations for such compounds in cancerous and non-cancerous livers and in other organs have resulted in the isolation of nonsaponifiable lipid extracts which, when tested in the subcutaneous tissues of mice, have yielded malignant tumors at the site of injection as well as in distant organs.

The carcinogenic factor of the nonsaponifiable fractions has been found to be a crystalline material consisting chiefly of cholesterol[27].

Primary Liver Cancer in Man. It is highly improbable that a common genetic factor is responsible for the enhanced incidence of the disease among such diverse and widely separated people as the indigenous races of Africa and the Orient. The Negroes of North America are no more subject to the disease than the American white population[28]. Moreover, there is strong presumptive evidence that frequency of the disease varies with environment even in the same race, since primary liver cancer appears to affect the Portuguese East African Bantu six times more frequently than the Bantu of South Africa, although there is little, if any, genetic difference between them[1].

Hepatic Cirrhosis and Primary Liver Cancer. Most observers regard the frequent coincidence of cirrhosis with primary liver cancer as an important intermediate stage in the carcinogenic process. Cirrhosis has been discovered in a large proportion of liver cancers throughout the world. In Africa and Asia, moreover, it is exceptional to encounter liver cancer without cirrhosis.

Cirrhosis appears to be associated more frequently with hepatocellular cancer than with cholangiocellular cancer. According to Ewing[29], cirrhosis is present in 85 per cent of hepatocellular cancers and in 50 per cent of cholangiocellular cancers. For both tumor forms, the association between the two diseases averaged 67 per cent, there being a range of 53 per cent to 100 per cent in a large series of cases compiled from the literature.

Postmortem Incidence of Cirrhosis. Where primary liver cancer is infrequent, hepatic cirrhosis is likewise relatively uncommon. In Europe and America the postmortem rate of cirrhosis is between 2 per cent and 3 per cent. Among the peoples of Africa and Asia, on the other hand, cirrhosis is found in 6 per cent to 10 per cent of all autopsies.

This relationship, however, is not absolute, for although a high incidence of infantile cirrhosis has been reported in certain parts of India, Ceylon, and Jamaica, liver cancer is relatively uncommon in these localities.

Hepatic Cirrhosis Developing Into Carcinoma. Most observers agree that cirrhosis precedes the onset of liver cancer. Malignant transformation appears to occur more readily in Africans and Orientals than in Western people.

In Europe and America primary liver cancer has been found in 3 per cent to 10 per cent of deaths from cirrhosis. In Africa the corresponding figures are 17 per cent to 43 per cent, whilst in Asia they are 12 per cent to 25 per cent.

Cirrhosis-Producing Agents and Liver Cancer. Because of its frequent association with primary liver cancer and its high incidence among the very races known to be prone to this tumor, cirrhosis is commonly regarded as an important precursor of the malignant process. On this account, a number of known cirrhosis-producing factors sometimes found in close association with human liver cancer have at different times been credited with possessing carcinogenic properties or acting as co-carcinogens on already damaged livers.

These factors include: 1) Intestinal parasites 2) liver flukes, which are said to elaborate substances that are toxic for the liver 3) schistosomiasis, which produces fibrosis around embolized schistosome ova 4) hydatid cysts 5) hepatic syphilis 6) infectious hepatitis 7) hemochromatosis and siderosis 8) alcohol 9) spiced foods 10) a keloid diathesis in Negroid races, among whom there is often a tendency towards

excessive connective tissue hyperplasia even after seemingly unimportant wounds.

Not one of these factors, however, is common to all communities known for their high incidence of primary liver cancer. Thus, liver fluke infestation, though common in China, Japan and other Oriental countries, is unusual in Africa; and although schistosomiasis is prevalent in many parts of Africa and Asia, primary liver cancer is rare in Egypt, where schistosomiasis is stated to affect 70 to 90 per cent of the Nile population, and is rare also among Western people living in bilharzia-infested areas. Moreover, infectious hepatitis appears to be no more frequent among Africans and Orientals than in Europeans or Americans. Africans do not, as a rule, eat highly spiced foods; on the other hand, the incidence of primary liver cancer is relatively low in Mexicans, yet their dietaries are rich in condiments.

Malnutrition and Cirrhosis. From clinical and experimental observations it would appear that chronic malnutrition, prevalent in parts of Africa and Asia, may be one of the more important causes of cirrhosis and perhaps also of primary liver cancer. Conversely, the general good state of nutrition prevailing in Europe and North America may perhaps account for the relative infrequency of these liver lesions. The diet of the African is often a deficient one. Depending upon geographic and climatic conditions, the staple foods are maize (corn) in southern Africa, and plantains, yams, potatoes and cassava in tropical Africa. Cattle, as a rule, do not thrive in central Africa, and are seldom slaughtered in southern Africa because they represent wealth to the rural Bantu,—also, their milk yield is poor. Moreover, among many African tribes, the consumption of fish, eggs and other protein-rich foods are forbidden by age-old tribal superstitions, traditions and customs.

In Indonesia and other parts of Asia known for their high liver cancer rates, the staple diet is rice; and the supply of meat, milk and other animal products is inadequate, because most of the available soil is used for the production of rice and other predominantly carbohydrate foodstuffs which offer a more generous caloric yield.

The common defects of all these high starch staple African and Asian foods are deficiencies in animal and other first-class proteins, in fats and in vitamins, especially of the vitamin B complex group. Carbohydrates are in excess.

For this reason, and also because of the seasonal fluctuations in food

supplies among Africans during the dry winter and early summer months, chronic malnutrition occurs and may manifest itself as an acute and sometimes fatal form of "kwashiorkor". This syndrome has been described in many parts of the world under different means. It is currently referred to as "protein malnutrition"[30].

Kwashiorkor is mainly due to lack in the diet of animal proteins and vitamins of the B complex group. It affects children during the breast-feeding, weaning or post-weaning periods, i.e., between the ages of six months and three or four years. The main clinical features include edema, ascites, retardation in growth and muscular wasting, lethargy, irritability, diarrhoea, various dermatoses, depigmentation of the skin, depigmentation and loss of texture of the hair, atrophy of the pancreas (in certain areas), and enlarged fatty livers which, in later life, may become fibrotic and culminate as a profound form of portal cirrhosis.

The histologic appearances of the fatty and fibrotic livers associated with kwashiorkor generally resemble those of experimental rats fed on the staple Bantu diet of corn meal and sour milk[31], and also those of rats fed on experimental diets deficient in the lipotropic factors, methionine or choline[32, 33]. Moreover, liver cancers have been induced in experimental animals by the sole means of choline-deficient diets unsupplemented by carcinogenic agents[34], and also by ethionine, the synthetic analog of methionine[35, 36].

It will be apparent, therefore, that primary liver cancer, so frequent among the populations of Africa and Asia, originates largely in an organ that is the seat of pre-existing hepatic fibrosis or cirrhosis and that the geographic and demographic distribution of both diseases is, to a large extent, identical, although there are notable exceptions.

The relevance of these observations lies in the influence of dietary factors upon the production of cirrhosis and primary liver cancers in experimental animals. Diets low in protein or in riboflavin not only induce cirrhosis, but also facilitate hepatic tumor formation in rats fed on these diets supplemented with dimethylaminoazobenzene ("butter yellow"), whereas high protein or riboflavin diets under similar conditions have the opposite effect.

If the results obtained in animals can be paralleled in man, it is reasonable to assume that human populations existing on deficient diets responsible for kwashiorkor can develop cirrhosis and other liver lesions

similar to those induced in animals under somewhat identical dietary deficiencies, and that accessory hepatotoxic or carcinogenic agents may likewise produce liver cancer.

However, no known external agents (e.g., similar to "butter yellow") have yet been isolated to account for human liver cancer. It must be remembered also that much of the evidence pertaining to etiology in human liver cancer is circumstantial, and that the actual cause of the remarkable sensitivity of the liver to cancer in African and Asian races has not yet been established. Neither the evolution of cirrhosis from kwashiorkor nor the exact mode of neoplastic transformation from active cirrhosis is as yet understood. A great deal of research is obviously necessary.

In cirrhosis and other liver damage, environmental factors additional to malnutrition are perhaps required to effect carcinogenesis, for there is as yet only scanty evidence that primary liver cancer can be induced by the sole means of a deficient diet. In Africa and Asia, it is possible that a susceptible liver already deranged by malnutrition may in this way become more vulnerable to other external stimuli, which may then have the effect of initiating the cancerous process. These adventitious agents may include endemic parasitic infestation, acute hepatic infections, tropical diseases, and irritation by known toxic substances or perhaps by some as yet undiscovered compounds with carcinogenic potentialities.

Absence of one or other such additional toxic factor may possibly explain the lack of correspondence between cirrhosis and liver cancer on the one hand, and malnutrition on the other, in Jamaica, Central America, and in other localities where kwashiorkor-like syndromes are present.

To determine whether primary liver cancer is a preventable disease (as seems likely) and in order to search for naturally occurring carcinogenic substances analogous to the azo-compounds or other chemical substances used in the experimental induction of liver cancers, local research should be conducted into the dietaries, customs and habits of those African and Asian populations showing the highest susceptibilities to liver cancer. Present day knowledge indicates that French West Africa, Portuguese East Africa, South Africa and Indonesia are perhaps the more likely regions for these investigations.

The possibility that environmental factors may cause cancer has

aroused considerable interest in many parts of the world, and has been a main topic of deliberation at recent international cancer conferences[37, 38]. Intensive research into the various facets of primary liver cancer in Africa and Asia is essential, for it is felt that the solution of the mystery surrounding this unique tumor will have profound effects on the whole problem of cancer.

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THE FATE OF SODIUM AND WATER IN THE RENAL TUBULES*

The Sixth Harlow Brooks Memorial Lecture

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ON MARCH 30, 1950—back in the Dark Ages, so to speak, of our present subject—some of our British colleagues banded together in what they called the Renal Association**. They referred to themselves facetiously as the "renologists". After listening to formal presentations in the comfortable quarters of the Ciba Foundation at 41 Portland Place, they ofttimes dined together in one of the better restaurants near Piccadilly, and on many such occasions we may accept that the cross-chop of conversation which rippled over the long table contained frequent references to salt and water.

The Renal Association is still active scientifically and, I hope, gastronomically. To my knowledge not one of its members has come to an untimely end, despite their preoccupation with a technically intricate subject and a consequent measure of what the uninformed frequently call absent-mindedness. Nor do I wish a single one of them any misadventure. I cannot, however, avoid a perverse temptation to speculate: What would have happened had a renologist, at about this time, suffered rude juxtaposition with a bus or taxi while on his way from Gower Street to dinner?

I construct the following sequence from the known habits of renologists. As the victim of this hypothetic traffic accident took his place before the Gates of Heaven, St. Peter would, I anticipate, hand him a piece of chalk, perhaps fluorescent red, and request him to draw upon the golden pavement a "typical mammalian nephron". Peering over the

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Studies related to this problem, carried out by the writer and his colleagues, have been aided by a grant (H-1172) from the National Heart Institute of the National Institutes of Health.

** The moving spirits in the Renal Association, which met quarterly, were Professor Kenneth Franklin, Dr. A. A. Osman, Dr. W. W. Payne and Mr. John Sophian.

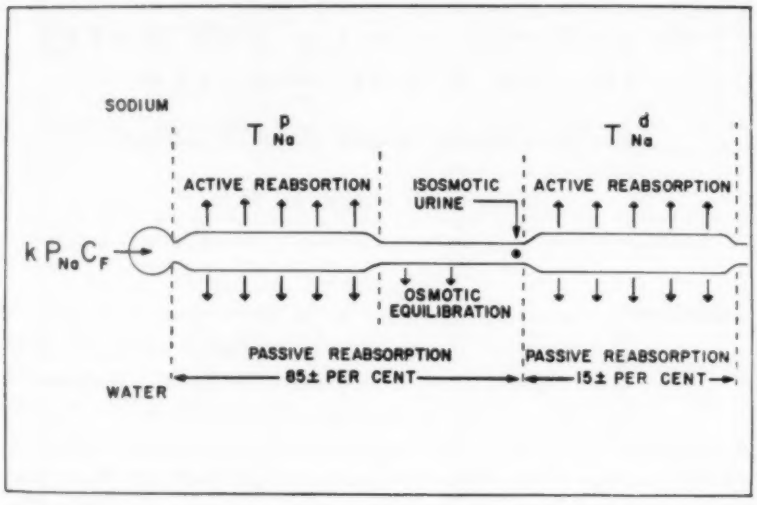

Figure 1—The rectilinear nephron, as previously drawn by the writer on several occasions with minor modifications.

renologist's shoulder as, on one knee, he begins his diagram, we follow the chalk as it inscribes a partially closed circle representing the glomerulus; and, extending to the right in a manner best described by Euclid's definition of a straight line, a tubule with a long, constricted part in the middle indicating the thin segment interposed between the so-called proximal and distal segments; and, lastly, a collecting duct (Fig. 1). Neither the ureter nor the bladder, nor, as a superior substitute, a ureteral catheter, is included, presumably because at that time these appendices appeared to possess no functional significance*.

Scarcely is the diagram completed, however, before its fluorescence is eclipsed in shadow as St. Peter also leans forward, his brow wrinkled, his eyes suggesting a venerable anatomist who is seeing something absolutely new, absolutely for the first time.

"And where in the world did you get that?"

The pavement artist puts the other knee on Heaven's floor and

* At low urine flows significant quantities of water and solutes diffuse across the ureter and bladder along their respective concentration gradients. Some diffusion may be predicated at unilateral flows in the dog at 1 ml/min., and diffusion becomes substantial at flows below 0.2 ml/min. Diffusion is most marked with respect to urea and water and requires revision of data based on bladder urine collected during oliguria[2].

fingers his chalk as he struggles to save what he divines is already lost.

"Why," he says with a show of confidence, "it's in the text-book—it's on page 732, or perhaps it's page 327—it's been in the text-book, at least in some of them, for a long time and—"

"No doubt, young man! There are text-books and text-books. But perhaps you should go back to some other text, say volume *ii* of that monumental work entitled *Handbuch der systematischen Anatomie des Menschen*, published in 1862 by the great anatomist Friedrich Gustav Jakob Henle*; or, if you do not read German, you might look into the 7th edition of the great English text, *Anatomy, Descriptive and Surgical*, published by Henry Gray in 1874."

"Oh, yes Sir! I know about Henle's loop, but *Karl* Peter, I think it was, in his monograph on the kidney implied, in effect, that Henle's loop is only an incident of organogenesis because—"

"And so! Did Herr Peter imply that an 'incident of organogenesis' need have no functional significance? Your cerebral cortex is also an incident of organogenesis!"

"No, but—"

The authority of the nacreous gates raised his hand. "I'm sorry, lad. Go back to the mammalian kidney and leave reductionist diagrams to—to the nuclear physicist. The chalk, please. And do come again."

And so it was that our renologist reappeared in London, perhaps never having been missed, certainly never knowing how narrowly he had missed out on Heaven.

Heaven for a renologist, I suppose, is a psychologic state characterized chiefly by certitude, of such a degree at least that he can say, "of this I am confident, so now I can go on to that". I have enjoyed few such ecstatic moments because of the skepticism of my colleagues, most of whom are veritable plagues in this respect. Indeed, my existence should perhaps be described as a sort of purgatorial nexus spun at the nodal points of doubt and certainty, its phasic interferences reminding me of the multiangular dinner conversation of the renologists. Which circumstance explains in part why, viewed objectively, I may seem to oscillate between dogmatism and disbelief, or to be seeking both poles at once.

* Henle[25, 13] (1862) incorrectly believed that the medullary loop was a U-shaped extension of a single convolution and thus comprised a closed system. Schweigger-Seidel[37] (1865) corrected this error by showing that the ascending limb, after additional convolutions, is connected with the collecting duct. von Kölliker was the first to use the expression "loop of Henle."

Perhaps I sat at dinner with our renologist in London in July of 1950, and perhaps I impressed him as a little too much in the heavenly confident mood. But I was at the opposite pole of doubt when, in August of that year, I drank several glasses of Carlsberg beer, at the XVIIIth International Physiological Congress in Copenhagen, with Heinrich Wirz of the University of Basle.

Henry had spent the academic year of 1946-47 with us, and now he had some exciting observations to show me. These observations concerned the mechanism by which the mammalian kidney elaborates a urine which is osmotically more concentrated than the blood. This operation is chiefly important in water balance when the available supply of free water is small. All vertebrates can excrete urine isosmotic with, or osmotically more dilute than the blood, but only the mammals (and to a lesser extent the birds) can excrete a hyperosmotic urine and thus compensate for a substantial deficit of water. Elsewhere I have suggested that the concentrating capacity of the mammalian kidney may have played an important role in our evolution, and specifically in the ultimate domination of the mammals over the dinosaurs and other reptiles at the end of the Mesozoic Era[36].

The elaboration of an osmotically concentrated urine requires that pure water, i.e., without any solute whatsoever, be removed from the isosmotic glomerular filtrate at some point along the nephron. In 1950 it was suspected that this operation may occur in the collecting ducts, but how it could be effected was a moot question—the only notion then available was that the epithelial cells could transport water molecules *per se* from the urine back into the blood. Since this must occur against a steep concentration gradient some sort of active transport must be involved, and no one was very happy with an hypothesis that invoked the active transport of water molecules[2].

The observations which Henry Wirz showed me consisted of measurements of the osmotic pressure at various levels in the rat kidney, determined in frozen sections by the melting point of ice crystals. He had used a micromelting-point method which is based on the fact that ice crystals are birefringent and light, while the water is dark, when examined by polarized light[11]. He had found that the fluids in the cortex were isosmotic with plasma, but the medulla showed a continuous increase in osmotic pressure from the cortical-medullary junction to the tip of the papilla (Figure 2). At any one level, no differences were

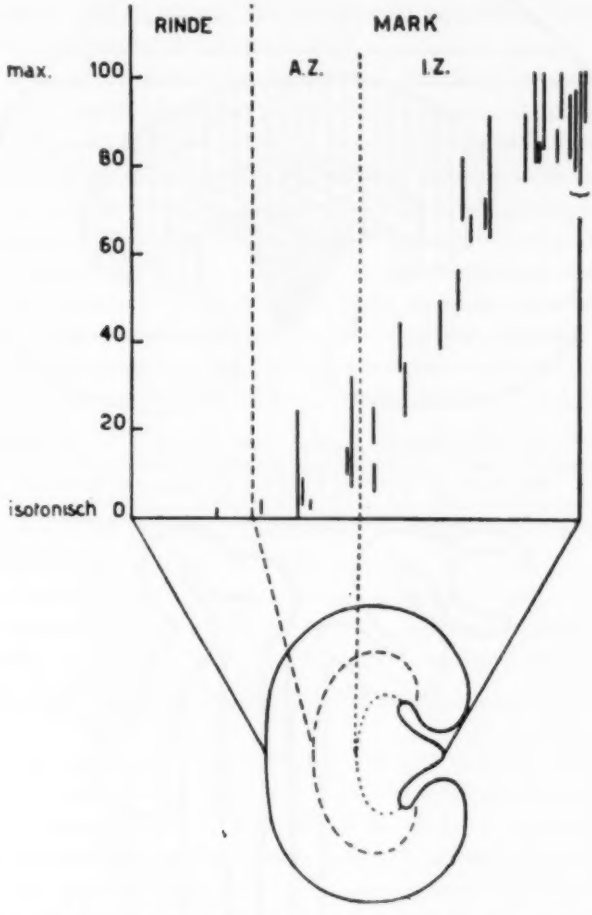

Figure 2—Osmotic pressure of the fluids in the kidney of the hydropenic rat, increasing from the isosmotic state in the cortex to reach a maximal value at the tip of the papilla. A. Z., outer zone, I. Z., inner zone of the medulla. This and Figures 3 and 4 are reproduced by permission of the authors and publisher[59].

discernible between the tubular urine, the capillary blood and the urine in the collecting ducts. This approach revealed the kidney to be composed of concentric shells, each of uniform osmotic concentration (Figure 3). To explain this surprising result, Wirz and his colleagues, Bartholomaüs Hargitay and Werner Kuhn of the University of Basle, had invoked a principle known as a countercurrent multiplier, wherein

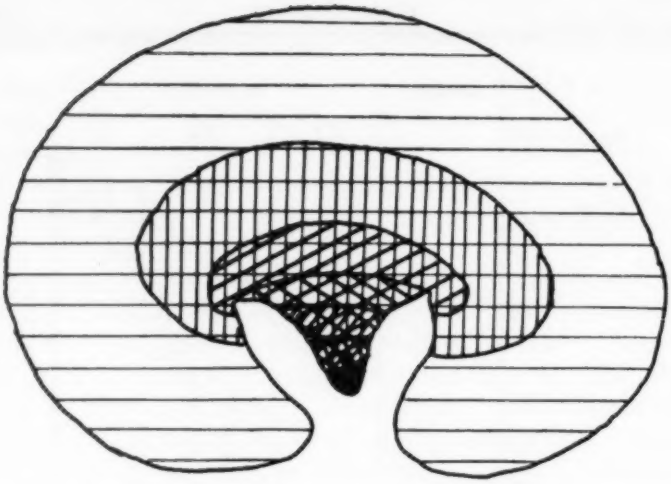

Figure 3—Regions of approximately equal osmotic pressure in the hydropenic rat kidney comprise concentric shells parallel to the corticomedullary boundary and medullary zones. As described by Wirz, Hargitay and Kuhn[20].

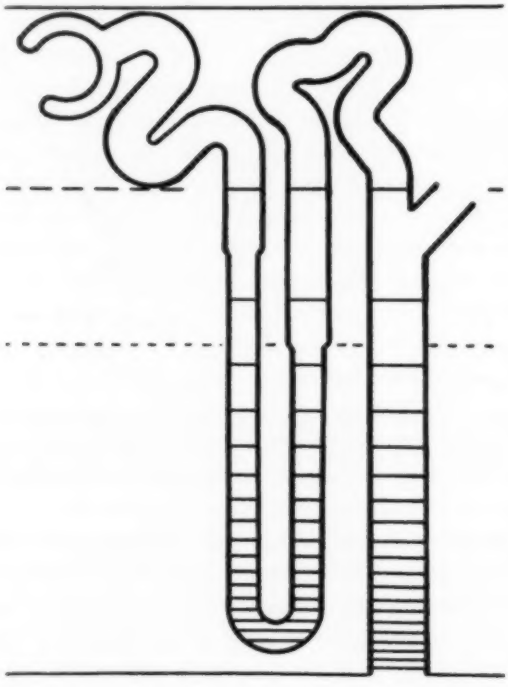

Figure 4—Variation of osmotic pressure in a single nephron and collecting duct. As described by Wirz, Hargitay and Kuhn[20].

the opposing streams in the descending and ascending limbs of the loop of Henle play an important role[50].

This was, at the time and for some time thereafter, very confusing. The countercurrent hypothesis placed the burden of concentrating the urine on the thin segment (which comprises the greater part of the nephron in the medulla), and by its structure the thin segment seemed scarcely able to support this burden. The hypothesis required that the collecting ducts be freely permeable to water and that the final urine be concentrated by the passive diffusion of water into the hyperosmotic interstitium established by the thin segments. It required that the tubular urine be concentrated at some point along the thin segment, only to be diluted again in the distal convolution, which teleologically seemed wasteful. And lastly, it required that all the blood traversing the medullary capillaries (*vasa recta*) be concentrated to exactly the same extent as the urine in the collecting ducts at any transverse level of the medulla, which meant more wasted energy (Figure 4). All this was difficult to believe, and I, for one, was inclined to question the micromelting-point method on technical grounds*.

In retrospect these criticisms are seen to be invalid: the micromelting-point method, inadequate as it then appeared, gave surprisingly good results, and a countercurrent hypothesis, in one form or another, is now an important chapter in renal physiology.

The basic principle of a countercurrent system is that two streams, moving in opposite directions, are so juxtaposed as to facilitate the mutual exchange of energy or substance in one form or another—what form is immaterial to the principle. Countercurrent systems may operate in one of two ways, as simple countercurrent exchangers, or as countercurrent multipliers. Countercurrent exchange systems (Figure 5) are widely used in engineering, but I doubt that the basic principle is patentable because nature invented it many millions of years ago. One example is presented by certain arctic birds which walk about on snow

* The fact that Hargitay and Kuhn[10] had developed the theory of the countercurrent multiplier in terms of an osmotic model which operated by means of hydrostatic pressure, and that no substantial hydrostatic pressure was available for this purpose in the loop of Henle, also handicapped the idea—though unfairly, as we now see.

Perhaps the major criticism in the writer's mind lay in the fact that ice has a substantial vapor pressure (3.013 mm. Hg at -5°C., 3.568 mm. Hg at -3°C., 3.880 mm. Hg at -2°C., 4.217 mm. Hg at -1°C., and 4.579 mm. Hg at 0°C., as compared with the vapor pressure of water of 12.788 mm. Hg at 15°C.), and diffusion, or more properly, sublimation of vapor across microscopic dimensions could lead to the equalization of osmotic pressure between the fluid in the collecting ducts and that in the medullary tubules and capillaries. Wirz[47] fully recognized the validity of this criticism as regards small distances, and it was perhaps because of sublimation that he failed to discover the dilute urine in the ascending limb of the loop of Henle.

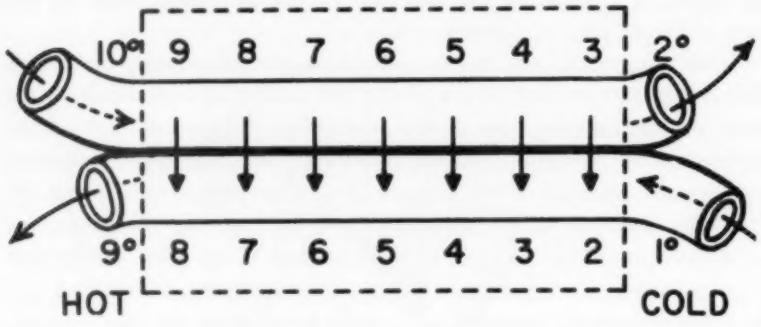

Figure 5.—A simple example of a countercurrent exchange system permitting the exchange of heat between two opposing streams initially at different temperatures. The system is conceived to be insulated externally. Note that in consequence of heat exchange both streams are warm at one end and cold at the other. Adapted from Scholander[35].

or wade in cold water. If the feet were near body temperature the heat loss would be considerable, but actually this loss is negligible because the feet may have a temperature close to that of the snow or water. Where the arteries and veins emerge from the body to enter the thigh they are intertwined complexly in a *rete mirabile*, this close juxtaposition of vessels facilitating the exchange of heat from the arterial to the venous blood; the arterial blood is thereby cooled and carries little heat into the foot, while the venous blood is thereby warmed and carries no large heat deficit into the body. A neat solution to the problem of how, at a trifling cost in calories, to maintain the body temperature and yet keep the feet refrigerated.

Claude Bernard in 1876 recognized the importance of heat exchange between the large arteries and veins in mammals, and many studies have recently been made by Irving, Scholander and others on thermal exchange systems in the limbs of various terrestrial and aquatic mammals (arctic dogs, porcupines, reindeer, caribou, beaver, muskrat, etc.), in birds and in arctic whales and seals*. The countercurrent exchange principle is utilized in the respiratory function of the gills as well as in the oxygen-filled swim bladder of fishes[15, 32-36, **].

* The surprising feature of this thermal exchange mechanism is its sporadic occurrence: a well-developed *rete* is present in the tropical sloth, manatee and whales, but absent in the cold water ducks, geese, sea gulls and swans; when present it may be related as much to heat dissipation as to heat loss.

**The swim bladder of the pelagic fishes contains oxygen at nearly 1 atmosphere pressure, as opposed to a partial pressure of one fifth of an atmosphere in the air and water, but in the deep sea fishes the oxygen pressure may reach 200 to 300 atmospheres, a 1000- to 1500-fold increase over the partial pressure of oxygen in the water.

The countercurrent multiplier differs from the countercurrent exchanger only in the fact that, besides adding and subtracting, it also multiplies, but the basic principle is not greatly different—you will recall from your ordinary calculating machine, if not from your elementary arithmetic, that you can multiply (or divide) by the simple expedient of adding (or subtracting) repetitively. The principle of the countercurrent multiplier has been applied in several studies since 1938 by Professor Werner Kuhn, Director of the Physical-Chemical Institute at the University of Basle. The principle operates in the rectification column of a distillation apparatus, and it has been applied by Kuhn and Martin to the development of the gas centrifuge and the separation of optical isomers from solution[28, 29].

It was one of Kuhn's graduate students, Bartholomaüs Hargitay, who first conceived of a countercurrent osmotic multiplier and its possible application to the kidney[10], though the final achievement represented the collaborative efforts of Kuhn, Hargitay and Wirz.

In the classical osmometer, hydrostatic pressure is used to equalize the vapor pressure (or activity) of a solvent across a semipermeable membrane. Any solution, however, may be further concentrated by dividing it between the two compartments of an osmometer (Figure 6) and applying hydrostatic pressure to one compartment (C_1), when solvent will be forced through the semipermeable membrane to dilute the fluid on the other side (C_2). The degree of concentration which can be effected in a single such operation by a given hydrostatic pressure is, of course, strictly limited in theory, but the process can be repeated indefinitely (in the ideal case) by removing the more concentrated solution (from C_2) and redistributing it between the compartments of a smaller osmometer and then reapplying the same hydrostatic pressure. Hargitay and Kuhn[10] calculated that after 20 such transfers, in each of which the volume is reduced by one half, one cubic meter of solution subjected to a hydrostatic pressure of only one tenth of its osmotic pressure will yield 0.48 ml. of a solution having twice the original concentration.

The novel feature in Hargitay and Kuhn's countercurrent system is the substitution, for this discontinuous step-wise procedure, of a continuous series of infinitesimal increments. Their basic theoretical model consists of an osmometer designed in the shape of a hair-pin or U-tube with a common wall consisting of a semipermeable membrane, the two

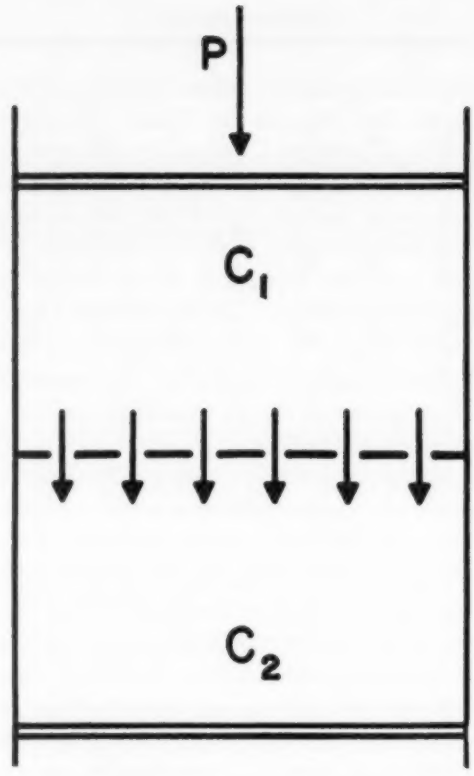

Figure 6—A conventional osmometer in which a hydrostatic pressure, P, increases the osmotic concentration of a solution in the compressed compartment, C_1, and dilutes it in a second compartment, C_2, beyond the semipermeable membrane.

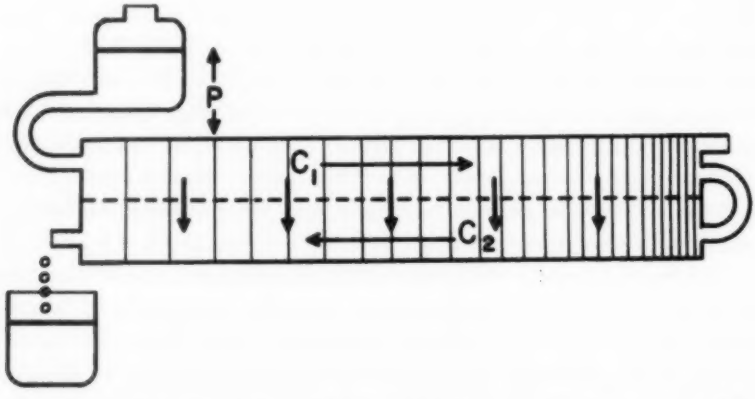

Figure 7—The hair-pin, continuously operating countercurrent multiplier as designed by Hargitay and Kuhn[9]. At the right are shown the capillary "reversal point" and an outlet for bleeding off small quantities of highly concentrated solution.

compartments being connected to each other at the far end by a fine capillary tube (Figure 7). After the compartments are filled with a suitable colloidal solution, circulation through the system is maintained by applying a constant hydrostatic pressure to one compartment (C_1), the other being left open to drain freely. The hydrostatic pressure in the first compartment is transmitted uniformly up to the capillary, or "reversal point", where in consequence of viscous resistance this pressure is abruptly reduced to a low value.

In consequence of the difference in hydrostatic pressure water will move from the upper to the lower compartment across the semipermeable membrane, but at any one point along the membrane equilibrium will be approached and the opposing fluids will have nearly the same osmotic pressure. Hence a fixed, limited hydrostatic pressure in C_1 will bring about additional filtration at each successive point, with the consequence that the osmotic pressure on both sides will increase along the length of the hair-pin, to reach its maximal value at the reversal point. In the eventual steady state this maximal osmotic pressure will greatly exceed that attainable by the same hydrostatic pressure in a static osmometer. The concentrated fluid can be bled off in small quantities at the reversal point without disrupting the process. Other things being equal, the narrower the compartments and the longer the apparatus, the more efficient will be its operation. (In the theoretical model developed by Hargitay and Kuhn (assuming certain finite dimensions), a 0.1 Osm solution could be concentrated to 2.0 Osm by a hydrostatic pressure of 3.75 atm.; to accomplish this in a single step would require 50 atm.).

In brief, the countercurrent multiplier effects only a small, theoretically limited change in concentration at any one point, but by additively imposing a new increment on the accumulated change at successive points, a final concentration can be attained at the reversal point which may be arbitrarily large and substantially greater than the theoretically limited local change. The operation is analogous to the compound interest law except that in the countercurrent multiplier the rate of increase is proportional to the *square* of the accumulated change.

Hargitay and Kuhn brought to the countercurrent osmotic multiplier some mathematics not customarily used by renologists, whose mathematics do not often go beyond the arithmetic required to keep a bank account. They also brought to the problem considerable mechanical

ingenuity in the construction of a physical model which consisted basically of two circular brass plates, each inscribed with a spiral groove 1 mm. deep, 5 mm. wide and 4 m. long; for a semipermeable membrane they used a sheet of commercial cellophane, and for a colloidal solution, sodium polyacrylate. This model converted a net filtration pressure into osmotic pressure with a multiplication factor of two-fold, a surprisingly good result considering the recognizable departures in the apparatus from ideal conditions*.

The countercurrent principle is applicable to any change of state, in the physical-chemical sense, and for the principle to apply to the kidney it is first required that the osmotic pressure of the interstitium of the medulla be increased. Hargitay and Kuhn recognized that this might be effected by the electro-osmotic movement of water into the tubular urine in the ascending limb, or conversely by the active reabsorption of salt (which for quantitative reasons must be sodium chloride) from the tubular urine in the ascending limb and the deposition of this sodium chloride in the interstitium—the change of emphasis from water to osmotic solute requiring only a change of sign in the basic equations[10, p. 554].

The evidence now available is convincing that a medullary countercurrent mechanism is involved in concentrating the urine, and that this same mechanism is involved in part in elaborating the dilute urine of water diuresis. This evidence can be most conveniently summarized by reference, in the first instance, to maximal antidiuresis in the hydropenic state.

Some of the most valuable of this evidence has been obtained by the exquisite and difficult micropuncture method which A. Newton Richards and his colleagues developed thirty years ago, and which investigators in Philadelphia and elsewhere have applied so resourcefully to the study of renal function.

In 1953 Wirz showed that renal papillary blood, collected by micropuncture of the superficial capillaries of the papilla in the golden hamster (which, like the kangaroo rat and some other rodents, has a long papilla extending well into the ureter) is essentially isosmotic with the bladder urine[46, 47], as is required by the countercurrent theory.

* It cannot be too strongly emphasized that in conceiving the application of the countercurrent multiplier to the loop of Henle, Wirz, Hargitay and Kuhn[10, 89] recognized that the *vis a tergo* in the kidney could not be hydrostatic pressure, and any tendency to impute to them a misconception on this point should be corrected.

However, information on the tubular urine was until recently confined to the convolutions near the surface of the cortex. The convolutions of the proximal segment represent about two-thirds of this segment: the last third is represented by the *pars recta* descending into the medulla and is not accessible to puncture. The distal tubule is accessible only in the convoluted portion beginning at the macula densa, where the straight ascending limb of Henle's loop makes contact with the vascular pole of the glomerulus of origin, and ending at its junction with the descending collecting duct. The collecting duct is accessible only in the tip of the papilla.

The studies of Walker, Bott, Oliver and MacDowell[44], reported in 1941, had shown that in the rat, guinea pig and opossum the fluid in Bowman's capsule and throughout the first half of the proximal tubule is isosmotic with the blood. It is clear that a considerable fraction of filtered sodium is reabsorbed in the proximal segment by an active transport process, osmotic equilibration being effected by passive diffusion of water[45]. (The argument that sodium and water are both reabsorbed proximally by diffusion along an osmotic gradient established by the colloid osmotic pressure of the plasma has been effectively answered by Berliner, Levinsky, Davidson and Eden[2].)

In the studies of Walker and his collaborators the evidence on the distal tubule was ambiguous. In 1956, however, Wirz[48] showed that at the beginning of the distal convolution (i.e., near the macula densa) the urine is distinctly hypo-osmotic to the blood even in hydropenic animals (the osmotic U/P ratio ranges from 0.5 to 0.8, and during NaCl infusion may decrease to 0.3)[9]; it attains the isosmotic state about half way along the distal convolution, but invariably remains isosmotic until it enters the collecting duct. It follows that the hyperosmotic state must be attained in the collecting duct itself.

These observations on proximal and distal urine have been fully confirmed in the rat and golden hamster by Carl Gottschalk and Margaret Mylle[8, 9] of the University of North Carolina. More importantly, Gottschalk and Mylle have shown in the hamster and kangaroo rat that during antidiuresis both the capillary blood (confirming Wirz) and the tubular urine collected near the tip of the loop of Henle have essentially the same osmotic pressure as the urine in adjacent collecting ducts at the same level*.

* Limited observations on *Psammomys obesus*, a North African rodent in which all nephrons have long loops, conform with the observations in the rat, which has both short and long loops[9].

Another valuable approach has been afforded by the analysis of cortical and medullary slices for specific solutes. That the chloride content of medullary tissue in the rabbit increases from the outer medullary zone (cortico-medullary junction) to the tip of the papilla has been known for many years[7, 26]. More recently Ullrich and Jarausch[42], of the University of Göttingen, have shown in hydropenic dogs that the concentrations of sodium, urea, exogenous creatinine and amino acids increase in a similar manner, though not all to the same extent: urea undergoes the greatest concentration and then, in decreasing degree, sodium, chloride, creatinine and amino acids*. Potassium (perhaps because it is not actively reabsorbed in the ascending limb), magnesium, calcium, and inorganic phosphate (perhaps because of their intracellular inclusion) do not show any concentration gradient between the outer medulla and the tip of the papilla.

These observations have been confirmed for sodium in studies using Na^{22} in the rat kidney by Krakusin and Jennings[20] of Northwestern University, and by direct analysis of sodium, chloride and urea in the dog kidney by Levinsky, Davidson and Berliner[23, 24] of the National Heart Institute. The rapid accumulation and the ultimate axial gradient of I^{131}-tagged albumin in the dog medulla, recently demonstrated by Lassen (then with the Institute of Mental Health), Longley (Institute of Arthritis and Metabolic Diseases) and Lilienfield (Georgetown University)[21, 25], conforms with this pattern; it is not known, however, how much of this albumin is contained in the capillaries and how much escapes into the interstitial fluid**.

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* During water diuresis sodium and chloride are concentrated slightly, urea very little, and creatinine not at all. These changes are hard to interpret because of the difficulty of attaining a steady state. Moreover the concentrations are expressed per ml. of tissue water—and in the diuretic kidney an unknown quantity of dilute urine is included in the distal tubule and collecting ducts. It is improbable that changes in sodium and chloride concentration reflect changes in the concentration in the tubular urine, but this circumstance may explain the behavior of creatinine. The interpretation with respect to amino acids, which are only slightly concentrated in the hydropenic animal, is even more difficult. The situation with respect to urea is discussed later.

Ulrich and Jarausch's statement that in hydropenia the urea concentration in the papilla (μmols/ml.) is equal to that in the urine must be qualified in light of the more recent demonstration by Levinsky and Berliner[22] that at low urine flows the composition of bladder urine is markedly altered by diffusion of water into, and of urea out of the urine across the ureters and bladder.

Ulrich, Drenckhahn and Jarausch[40] have concluded from the osmometric (swelling) method that the osmotic pressure of kidney slices follows the pattern described by Wirz, Hargitay and Kuhn, and which is to be expected from their analyses. It is well known, however, that the determination of the osmotic pressure of tissues by this method is unreliable; moreover, in this particular instance Berliner, Levinsky, Davidson and Eden[2] have found that fresh slices of medulla swell even in very hypertonic sucrose solution. The only seemingly reliable method for measuring the osmotic pressure of a tissue en masse is that of Maffly and Leaf[27]; this method reveals the medulla to be grossly hyperosmotic to the blood (skeletal muscle, liver, heart and brain are isosmotic), but quantitative interpretation is still complicated, even in hydropenic animals, by the presence of dilute urine in the ascending limb.

** Albumin reaches 85 per cent of its 60 minute concentration in 3 minutes, and the fact that I^{131}-tagged γ-globulin is concentrated much more slowly suggests that albumin escapes more rapidly from the capillaries.

So much for evidence. As for theory, at the time (1951) when Hargitay and Kuhn[10] published their paper on the countercurrent theory, and Wirz, Hargitay and Kuhn[50] on the kidney, nothing was known about the composition of the urine between the proximal convoluted tubule and the renal pelvis, and the physiological characteristics of the loop were not spelled out. It was posited that the "single" or initial effect, or *vis a tergo*, of the countercurrent system in the medulla consisted either of the movement of water from the descending into the ascending limb (which virtually amounts to active water transport), or conversely of salt (sodium chloride) from the ascending to the descending limb; they failed, however, to recognize that the latter mechanism could not operate as an osmotic multiplier unless the permeability of the ascending limb to water is restricted*.

After Wirz in 1956 had demonstrated the osmotically dilute nature of the urine in the early distal convolution in hydropenic animals, he recognized that the ascending limb of the loop must be relatively impermeable to water and he favored the belief that this dilution was effected by the reabsorption of sodium chloride in this segment (he did not distinguish between the ascending thin segment and the thick segment which extends from the inner zone of the medulla up to the macula densa). The permeability characteristics of the descending limb were not specified, though it was clear that sodium chloride must gain access to (and probably water lost from) this limb if the system is to work as a countercurrent multiplier. As in the original paper, it was posited that the progressive accumulation of sodium chloride along the long axis of the loop increased the osmotic pressure of the interstitium and concentrated the urine by passive abstraction of water through the collecting ducts[48,49].

Recognizing the theoretical difficulties of the 1951 description, and discounting Wirz' necessarily tentative suggestions of 1956, Robert Berliner and his colleagues[2] in 1958 proposed that sodium chloride is actively reabsorbed throughout the length (descending and ascending limbs) of the thin segment, and, as a necessary corollary, that this segment is everywhere essentially impermeable to water. Here the loop does not operate as a countercurrent mechanism in any sense, though

* Wirz, Hargitay and Kuhn[50] said that they did not observe an osmotic pressure difference between the structures at any given level, but that there does exist a *small* osmotic pressure difference (presumably too small to measure), underlining the word "small" for emphasis. This statement could imply some water impermeability in the ascending limb.

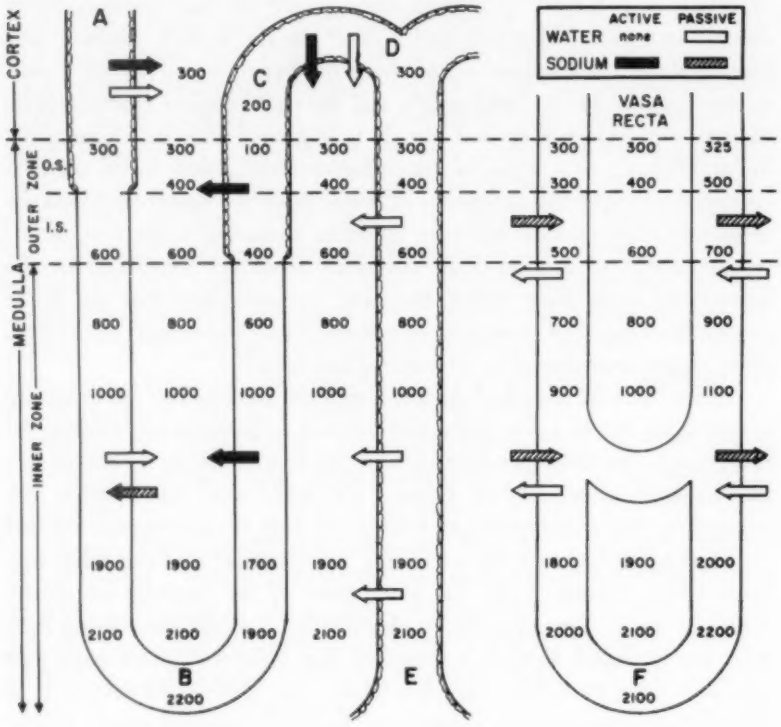

Figure 8—The loop of Henle as a countercurrent osmotic multiplier, basically as conceived by Gottschalk and Mylle[2]. Sodium chloride is actively reabsorbed in the ascending limb of the loop of Henle; the hyperosmotic interstitium abstracts water from the water-permeable descending limb (and possibly sodium chloride diffuses into this limb), thus increasing the concentration of sodium in the tubular urine delivered to the ascending limb and converting the system to a countercurrent multiplier. Since an osmotically dilute fluid is delivered to the distal convoluted tubule, the ascending limb must be relatively impermeable to water. (Reprinted by permission, Amer. J. Physiol.)

The system operates to establish an osmotic concentration gradient in the interstitium, increasing from the corticomedullary junction to the tip of the loop, and to concentrate the urine by the passive abstraction of water through the water-permeable collecting ducts. The *vasa recta* (right) serve as countercurrent exchangers, promoting the overall efficiency and carrying away in the ascending capillaries the water abstracted from the urine.

Sites for which data on the osmotic pressure of the tubular urine are now available: A, proximal convoluted tubule (cortex); B, tip of loop of Henle in papilla; C, distal convoluted tubule near macula densa, and D, near entry to collecting duct; E, papillary urine; and F, blood in the capillaries near tip of the papilla. O. S. outer stripe, I. S. inner stripe of the outer zone of the medulla. The figures are nominal estimates of osmotic pressure (in mOsm/kg. water) given by Gottschalk and Mylle.

the *vasa recta* continue to serve as contercurrent exchangers. In this hypothesis, however, the urine at all points around the loop should be hypo-osmotic to the blood in consequence of the removal of sodium, and the recent and contrary demonstration by Gottschalk and Mylle[8] that the urine at the tip of the loop is actually isosmotic with the urine negates this otherwise attractive theory.

The interpretation proposed by Gottschalk and Mylle[9], which fits the facts recited to this point, is that sodium chloride reabsorption begins in the ascending limb of the thin segment (Figure 8) and continues in the thick segment of the ascending limb and throughout the distal convolution. The entire ascending limb (thin and thick segments) is conceived to be relatively impermeable to water, thus assuring delivery of a dilute urine to the distal convolution. (The fact that infusion of NaCl increases the degree of hypotonicity of the distal urine is strong evidence that the loop does in fact reabsorb sodium at some more proximal region, and that it operates on sodium rather than on water *per se*.) As a working assumption, the descending thin segment is conceived to be permeable to water (and possibly sodium chloride), as was implied by Wirz[49]*; by this postulate the descending urine will come into osmotic (and sodium?) equilibrium with the interstitium, the system will serve as a true countercurrent multiplier, and the osmotic pressure of the interstitium will increase along the axis of the loop to reach a maximal value at the tip, or the "reversal point", which we may take to be the point where the water- and sodium-permeable descending limb gives way to water impermeability and active sodium reabsorption in the ascending limb. Again, of course, passive diffusion of water out of the collecting ducts serves to concentrate the urine, and the *vasa recta* (right of Figure 8), being in free interchange with the interstitium, serve as countercurrent exchangers, promoting the efficiency of the system and carrying away the sodium chloride reabsorbed locally and the water abstracted from the urine**.

This is essentially the hypothesis formulated by Wirz in 1956[48, 49]

* The question whether the descending and ascending thin segments are permeable to urea raises some difficult quantitative problems which can perhaps be answered only by micropuncture and direct analysis.

**Maximal concentrating effect will be achieved when flow through the collecting ducts is small relative to flow through the loop, when local sodium reabsorption is relatively large, and when blood flow through the *vasa recta* is relatively small.

It may be noted that though anastomoses never connect the descending and ascending limbs of the nephron, lateral anastomotic channels frequently connect the two limbs of the *vasa recta*[9].

but now spelled out in more detail and supported by direct analysis of the urine at the tip of the loop of Henle—the all-important datum required to substantiate a countercurrent hypothesis. Neither here nor in previous theories is there any requirement that the tubular or vascular channels be physiologically juxtaposed because lateral diffusion over microscopic distances can effect sodium and water equilibration.

I still do not like it: it seems extravagant and physiologically complicated—though so is the whole glomerular filtration-tubular reabsorption pattern. Only about one in seven nephrons in the human kidney have long loops, and not all of these have an extended thin segment in the inner medulla because many turn in the outer zone; the remainder are so-called cortical nephrons which at best reach the outer zone of the medulla, while many, perhaps most, turn in the cortex and in these the thin segment is very short or entirely absent[30]. In the dog, however, all the nephrons have long loops and long thin medullary segments[39]; yet the difference in concentrating power between dog and man subsisting on a mixed diet is not equally impressive. Least of all, however, do I like to see the squamous epithelium of the thin segment freely permeable to water (if not to sodium also) in the descending limb, only to acquire water impermeability and active sodium transport at the tip of the loop for no better reason, apparently, than the circumstance that it has turned a corner. But I suppose that I can get used to that, too.

But the problem may be more—or less—complicated than this.

Jarausch and Ullrich[16] have inserted microcatheters up the collecting ducts in the hamster kidney and examined the urine at two different levels in these ducts. Hilger, Klümper and Ullrich[14] confirm that the osmotic concentration increases along the length of the ducts; but more importantly, by reference to the concentration of inulin, they conclude that the ducts also actively absorb sodium from the urine*. These and other observations[43] lead these investigators to dismiss the thin segment as playing only a passive role in the concentrating mechanism—in effect they treat it as freely permeable to water, sodium chloride, urea, and presumably other solutes in the interstitium. They suggest that the "initial concentrating effect" in the concentrating operation is the reabsorption of sodium chloride in the thick segment of the ascend-

* The ducts also participate in K^+:Na^+ ion exchange, according to Hilger, Klümper and Ullrich's observations, and in NH_4^+ secretion[41].

ing limb (outer medulla) whereby the urine is diluted and the interstitium is enriched osmotically. Sodium reabsorption by the collecting ducts also enriches the sodium content of the inner medulla, a process which they call the "terminal concentrating effect". These two operations, they believe, suffice to concentrate the urine.

This interpretation has the advantage of shifting active sodium reabsorption out of the thin segment, but it presents several difficulties. If we assume that, at any specified level, the urine and interstitium are approximately in osmotic equilibrium, relatively more sodium than water must be removed from the urine in the collecting ducts if the interstitial osmotic concentration is to be increased, and this operation alone would serve to dilute rather than concentrate the urine inside the duct; it is difficult to see how transportation of sodium and/or water along the medullary axis in either direction, whether in the permeable thin segment or the *vasa recta*, could change the algebraic sign of this net operation. Second, it is not clear how sodium reabsorption by the thick segment and the collecting duct together could lead to an osmotic (and sodium) gradient which increases along the axis of the loop from the outer medulla to the papilla unless sodium reabsorption by the collecting duct is of some very large order of magnitude.

Assuming that the progressive increase in sodium (and chloride) concentration down the long axis of Henle's loop finds a satisfactory explanation in a countercurrent system, some subsidiary postulates may be required to explain the roughly parallel progression in concentration of exogenous creatinine, albumin, and perhaps amino acids. Inasmuch as the hair-pin pattern of the *vasa recta* affords a countercurrent exchanger, it is conceivable that the more rapid diffusion of water molecules between the tops of the capillary loop might create a sump in which more slowly diffusing solutes are dynamically trapped and held by continuous recirculation*. But this is very speculative, and in any

* Gottschalk and Mylle[9] suggest dynamic trapping to explain the increase in red cells observed in the *vasa recta* at the tip of the papilla; their reference here, however, is to the movement of protein-free fluid between the capillaries in compliance with the difference in plasma protein osmotic pressure, rather than to water molecules. But when they speak of the trapping of sodium, urea, and other diffusible solutes in the medulla, differential molecular diffusion seems to be implied.

All assumptions concerning permeability of the descending limb of the loop of Henle (or of the collecting ducts) to exogenous creatinine come into conflict with the observed osmotic U/P ratio in the papilla, the observed fraction of filtered water (*ca.* 1/8th) normally available for water diuresis in the dog (and man), and the observed constancy of the creatinine/inulin clearance ratio (1.0) in the dog, and are best avoided at this stage of the theory. This presents only one of several unresolved obscurities.

case it will not explain the fact that, relative to the cortex, urea is concentrated in the medulla to a much greater extent than the other substances studied.

This high papillary concentration of urea finds its explanation in the recent evidence presented independently by Levinsky, Davidson and Berliner[23, 24] and Klümper, Ullrich and Hilger[18] that in the hydropenic animal the collecting ducts are relatively permeable not only to water but also to urea. When urine is collected from the renal pelvis in the dog (avoiding diffusion across the ureters and bladder [see footnote p. 306*] the urea concentration (μmol/ml.) in the inner medulla ranges from 60 to 90 per cent of the concentration in the urine, and changes in the latter are invariably reflected by changes in the former in a variety of conditions (reduced filtration rate, low protein diet, mannitol and urea diuresis). This has the extraordinary consequence that the medullary urea and urine urea almost balance each other osmotically; in assessing the intrinsic osmotic operation of the loop of Henle some 60 to 90 per cent of the urine urea (and the osmotic pressure attributable thereto) must be ignored—in other words, correspondingly less osmotic work is required for the excretion of urea, and a given osmotic load of urea entails a correspondingly smaller excretion of water in the urine than does an equal osmotic load of sodium chloride, mannitol, etc., to which the collecting ducts are impermeable. Hence it was (as Berliner and his colleagues emphasize) that Gamble, McKhann, Butler and Tuthill[4] in 1934 noted the "remarkable economy in renal function referable to urea".

Three attractive features of the countercurrent hypothesis have been noted by all investigators. First is the fact that the urine is concentrated by an osmotic gradient down the long axis of the loop, with only a small gradient across any one cell layer in the loop. Second, the hypothesis dispenses at long last with the active transport of water molecules—the entire operation is mediated by the active transport of sodium chloride, a process that to one degree or another is going on throughout the length of the nephron. The third attractive feature is that, for the same mechanism (sodium chloride reabsorption) to serve either to concentrate or to dilute the urine, only a redefinition of the locus of action of the antidiuretic hormone (ADH) may be required.

It is widely accepted that the action of ADH is "permissive", in that

it simply promotes passive osmotic equilibration between the tubular urine and the blood by increasing the permeability of the "tubular" epithelium to water. Sawyer[31] and Wirz[49] have independently attributed this action to the opening of hypothetical "pores" which facilitate the diffusion of water, in a manner analogous to the action of the neurohypophysial water-balance principle on amphibian skin, as demonstrated in 1952 by Koefoed-Johnsen and Ussing[19]. Without specific reference to this "pore" theory, Ginetsinsky, Ivanova, Sax and Titova[5, 6] of the Institute of Evolutionary Physiology, Academy of Sciences, Leningrad, USSR, have suggested that ADH liberates hyaluronidase in the tubules and that this enzyme depolymerizes the hyaluronic acid cement between the epithelial cells and lets water pass through.

That ADH has no action on water reabsorption in the proximal convoluted tubule has been demonstrated by Wirz[49] and Gottschalk and Mylle[9]. These investigators have also demonstrated that in the early distal convoluted tubule the urine remains osmotically dilute (osmotic U/P ratio = 0.3 to 0.6) even in the hydropenic state, showing that ADH has no major action on the permeability to water of the ascending limb of Henle's loop or on the early distal convoluted tubule itself*. (Action on the descending limb of Henle's loop, a possibility suggested by Wirz, has not been excluded.)

It has been noted that during antidiuresis osmotic equilibration between urine and blood is attained from the middle of the distal convoluted tubule on, the urine remaining isosmotic until it enters the collecting duct. In water diuresis, however, the urine remains dilute throughout the distal convolution; and, in fact, both Wirz[49] and Gottschalk and Mylle[9] find that it appears to be further diluted between the end of the distal tubule and the bladder. Though these observations comprise "spot" anatomical tests and cannot exclude the mixing of urine of different composition from various nephrons, further dilution in the collecting ducts may reflect active sodium reabsorption in these ducts. One fact is clear, however, and that is that in water diuresis the collecting ducts are relatively impermeable to water.

The simplest interpretation of these data is to suppose that the locus of (the "pore") action of ADH extends from the early part of the distal convoluted tubule all the way down the collecting ducts[2, 9, 14, 31, 49].

* del Greco and de Wardener,[8] Berliner and Davidson[1] and Kleeman, Maxwell and Rockney[17] have shown that the concentrating mechanism continues to operate (though at an undetermined level) in the absence of ADH. However, Gottschalk and Mylle[9] suggest that ADH may somehow promote the activity of this mechanism.

Hence, in the absence of ADH all (or nearly all) the osmotically free water generated by the reabsorption of solutes – primarily sodium chloride – in the loop of Henle and the distal segment remains to be delivered to the collecting ducts; since these are relatively impermeable to water in the absence of ADH and therefore isolated from the hyperosmotic medulla, this free water emerges from the kidney as a copious volume of dilute urine.

Here I must pause to express my admiration for the painstaking and resourceful investigations that have bridged the gulf between 1950 and the present position of renal physiology. And I happily add that in this presentation I have had the good fortune of correspondence with Henry Wirz and access to unpublished manuscripts by Dr. Gottschalk, Dr. Berliner and their colleagues, as well as the opportunity for numerous personal discussions, for all of which I am deeply grateful.

I was not in so favorable a position last spring when I received a letter which started about as follows:

"Dear Dr. Smith: I am one of a handful of students in the first year class of Harvard Medical School who are confused about the Wirz, Hargitay and Kuhn countercurrent theory, and wonder why you fail to mention it in your *Principles* [of 1956]. . . ."

In a brief, elementary work one hews as narrowly as possible to the line of close-to-heavenly certitude, and I could have best replied:

"Dear Mr. Davidson: I am also confused. . . ."

Today I would answer that I believe that a countercurrent system–probably a multiplier–operative in the loop of Henle is here to stay; but the basic postulations with respect to the physiological activities of various segments, not to mention issues that arise from comparative anatomy, pathological physiology, embryology, and what-not, are still a little confusing . . . and so with respect to the fate of sodium and water in the renal tubules I still oscillate between the poles of purgatorial doubt and heavenly certitude–between skepticism and dogmatism, the one always uncomfortable, the other, unprofitable.

When St. Peter interrupted him, our renologist was about to say, "–but in 1956 Smith drew the nephron in a straight line!" Of course this weak appeal to authority would have availed nothing before the Great Empiricist, but I promise you that Smith will not draw it that way again–even if he has only the foggiest notion of how it should be drawn!

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MEGACYSTIS AND MEGA-URETER IN CHILDREN*

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This paper is concerned with the relationship between the enlarged bladder and the chronically dilated ureters so commonly found in children. Some of these cases seem to fall into the mega-ureter group, as distinct from the known obstructions, but it is important to realise that the term mega-ureter at present covers a variety of conditions.

In many examples of mega-ureter, the bladder is not involved in any way: the ureteric orifice is normal, vesico-ureteric reflux is absent and micturition is unaffected. In others, reflux is present during complicating attacks of infection, and the ureters at that time appear grossly dilated, yet if the urine can be kept sterile by chemotherapy over the course of a few years, the ureters become normal in calibre and reflux is no longer demonstrable. I am not here concerned with either of these forms of mega-ureter, but with the group of children who have bilateral mega-ureter, free vesico-ureteral reflux and an apparent enlargement of the bladder. Quite a number of these cases have been recorded in the literature under various names: I am accustomed to use the term mega-ureter–megacystis syndrome, a descriptive title which does not commit me to any specific view of the pathology. A characteristic of these children is that, except during exacerbations of infection, they are apt to pass urine rather infrequently–perhaps only twice in 24 hours–but they pass a large volume of urine at one time. The *megacystis* is a functional enlargement of bladder capacity, distinct from the distention of accumulating residual urine characteristic of urinary obstruction. However, the mega-ureter–megacystis cases do at times go into retention, and the differentiation of the various causes of bladder enlargement constitutes the chief point of discussion: that a differentiation is possible. I hope to demonstrate this by describing our observations on bladder

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size and bladder activity as revealed by cystometrograms and cine-radiology.

When we come to study the behaviour of the congenitally obstructed bladder, we immediately encounter the difficulty of making a certain diagnosis in the most numerous group—the bladder-neck obstructions. It is clear that this diagnosis has a different significance in different urological centres: in some, it is a common and usually a mild disease, occurring with almost equal frequency in children of both sexes; in others, it is rare and grave, and almost confined to the male. Emmett and Simon[1] (1956) have reported on the common disorder: most of the children in their group suffered from enuresis and recurrent urinary infection, residual urine was often small or absent and the chief criterion of diagnosis was that the bladder-neck "looked obstructive". Kjellberg, Ericson and Rudhe[2] (1958) in Stockholm, on the other hand, found only six examples of bladder-neck obstruction among over 11,000 cases of lower urinary tract disease in children. In these the obstructive factor was severe, and responsible for vesical retention and advanced hydronephrosis. The obstruction was believed to be situated at the bladder-neck because the urethra was itself radiologically and endosocopically normal.

It is true that bladder-neck hypertrophy is a common finding in all cases, but the minor degrees of hypertrophy are not always easy to identify beyond dispute on endoscopy, and a major hypertrophy can be found in many congenital obstructions of the urethra below the bladder-neck. In a typical urethrogram from a case of congenital posterior urethral valves, the urethra above the valves is dilated, but at the bladder-neck a filling defect is produced by the thickened internal sphincter. The musculature here hypertrophies along with the detrusor as a whole, and in order to attribute an obstructive significance to this hypertrophy, we must first exclude obstruction lower down. My colleague, Dr. Bodian[3] (1957), pathologist at the Hospital for Sick Children, Great Ormond Street, has recently made some important observations in this field: he has found a change in the nature of the urethral wall in cases where the clinical diagnosis would be bladder-neck obstruction. The normal posterior urethra in the male infant is a muscular tube with a small area of glandular prostatic tissue. In the so-called bladder-neck obstruction case, there is a large area of fibrous and elastic tissue, replacing the normal glandular elements, and forming a sheath

for the whole urethra from the bladder-neck above to the corpora cavernosa below. The bladder-neck musculature is indeed hypertrophied along with the rest of the detrusor, but it was postulated that the fibro-elastosis sleeve, by preventing the normal relaxation during micturition, constituted the obstruction, while the bladder-neck hypertrophy was secondary. As in the urethral valves, it was the effect, not the cause of the obstruction. The ordinary wedge resection would reach only the upper part of the fibro-elastosis sleeve, so that the histological changes are not easily identifiable in such biopsies, and indeed were not recognised in our experience until whole postmortem sections were mounted.

While Dr. Bodian was engaged on this work, I had been giving a trial to the plastic operations on the anterior urethro-vesical junction, for I had been dissatisfied with the results of the ordinary resection in cases of infants suffering from a severe chronic retention. In particular I was using the Y-V plasty, as I still do, and I was therefore able to provide biopsy strips from a considerable length of the anterior wall of the prostatic urethra. Bodian has found the fibro-elastosis lesion in some, but not in all, cases that I would have labelled bladder-neck obstruction. The "positives" have been children with severe obstruction, heavily trabeculated bladders and dilated ureters, but often normal ureteric orifices. The urethrograms—usually attained by expression in the unconscious child—were either normal, or showed a slight tapering dilatation, contrasting with the bulging outline of the posterior urethra in the valve cases. The "negatives" occurred in cases of large solitary vesical diverticula without generalised trabeculation, whose primary abnormality I believe to be herniation of mucosa through a gap in the musculature. Other "negatives" showed very large bladders with slight or absent trabeculation—cases which I place in the mega-ureter – megacystis group, and which we shall discuss later on.

We feel then that the fibro-elastosis, rather than a true bladder-neck obstruction, is the pathological basis of "Marion's" disease—the congenitally obstructed bladder without evident change in urethral calibre. There may be a disease of bladder-neck obstruction which accounts for the mild cases, particularly in the female, but we do not think that the severe disorder can be attributed to a neuromuscular coordination, or to any other dysfunction of the internal sphincter itself. The identification of fibro-elastosis by biopsy gives us one tool in sorting out the en-

Fig. 1. Range of bladder capacities as measured by cystometrogram in various conditions: Simple mega-ureter (13 cases); Bladder-neck obstruction (7 cases); Posterior urethral valves (7 cases); Mega-ureter-megacystis syndrome (14 cases); Absent abdominal muscles (3 cases).

larged bladders, but it is a little uncertain and we badly need a preoperative diagnosis. We have, therefore, explored the possibilities of using bladder capacity, determined by cystometry, as another tool. Cystometry has unfortunate limitations; it cannot be conveniently employed in children under the age of three years or in unaccommodating children over that age, since it requires some cooperation from the subject. This is particularly disappointing since so many of the cases in which we are interested present the problem in early infancy. The bladder capacity, as registered by cystometry, depends partly upon the rate of inflow, and we have employed a standard of 150-200 drops per minute. As far as possible, all our cystometrograms have been undertaken by one research worker—Dr. Leibovitz. Between three and 13 years, the age of the child has made much less difference to the capacity than other factors. In our cases as in other reports, the normal capacity is between 100 and 250 ml. There is a small percentage of normals over this and we have taken 450 ml. as the absolute upper limit of normal.

In the case of the obstructed bladder, the volume with which we have concerned ourselves has been the capacity after relief of retention. In both the urethral valve cases and the so-called bladder-neck obstructions, of the fibro-elastosis type, the bladder has shown surprisingly little increase of functional capacity (Figure 1). It seems that the normal effect of congenital obstruction is to produce gross detrusor hypertrophy, not extreme dilatation, so that once the obstruction is relieved, and residual urine eliminated, the volume passed at any act of micturition is little greater than normal—in fact, frequency and urgency due to an irritable musculature may make that volume smaller. These findings for the congenital obstruction might well be paralleled in the prostatic obstruction of the elderly, and, in general, suggest that if a bladder has a very large functional capacity, we must find a cause other than obstruction, or a good reason for an unusual response to obstruction.

These large bladders we find in the mega-ureter—megacystis group. The children have gross bilateral ureteric dilatation with free reflux into the ureter, which occurs as soon as the bladder is filled—not simply on micturition. Cystoscopy shows an apparently normal bladder in most; there is little or no trabeculation, but the ureteric orifices are widely dilated. If watched, these orifices will be seen to contract vigorously from time to time, and on occasion will momentarily have an

almost normal appearance. Powerful, though perhaps not very useful, contractions are even better observed if a urethroscope is introduced through the dilated orifice, and the effects of the irrigating stream observed. The urethra appears normal radiologically and endoscopically. Most of these cases have histories of recurrent urinary infection, and apart from these attacks, the characteristic disturbance of micturition has been infrequency, and passage of a large volume at each micturition. Cine-radiological studies have been carried out in a number of these cases and reveal a most interesting state of affairs. At each act of micturition the bladder contracts normally and empties completely, and the bladder shadow is altogether obliterated; but the vesico-ureteral reflux allows a large proportion of the urine expelled to run upwards into the ureters. A short while after micturition, as the bladder relaxes, this ureteric urine returns to re-distend the bladder, and if an ordinary measurement of residual urine were made, a considerable volume would be found. This is, however, a "false" rather than a "true" residuum, since it does not indicate a failure of bladder contraction. Moreover, a second and third micturition will result in more urine being expelled per urethram—an important point in diagnosis and treatment, since the ability to perform double micturition must indicate reflux into ureter or diverticulum, while the more satisfactory elimination of urine effected reduces the liability to recurrent infection.

A child with such easy vesico-ureteric reflux can be precipitated into acute retention by anything which raises the level of urethral resistance above that of the ureteric resistance—as, for instance, by post-instrumentation edema or by infection. When first seen in the retention phase, the similarity of these cases to "bladder-neck obstruction" is naturally very great, and it is in these that the study of bladder capacity is most interesting.

The large volumes do not occur in those cases with normal ureteric orifices and slight or absent reflux, which I call simple mega-ureter, and it may be objected that what we are measuring in the megacystis cases is not simply bladder volume, but ureteric volume as well. It is certainly true that the bladder is not quite so large as the cystometrograms indicate, as can easily be demonstrated by repeating the investigation after an operation to prevent reflux at the ureterovesical junction. However, a hand on the abdomen at the end of the investigation will quickly dispel any doubts about the bladder enlargement. Moreover, these

mega-ureter–megacystis cases are capable of passing large volumes–a boy of 13 years regularly passed 600 ml., for instance; and the volume passed in any one act of micturition is less than the total bladder capacity because of loss up into the ureter. By contrast, reflux in late cases of bladder-neck obstruction is common, but does not result in greatly increased cystometrographic readings.

Granted, then, that there is a megacystis, a bladder of enlarged functional capacity, we naturally ask whether this is the primary abnormality, perhaps of the same nature as the mega-ureter, or whether the enlargement is secondary to some other lesion. A neurological disorder must be considered, and Swenson and his colleagues, describing apparently similar cases, claim that there is a diminution in the number of ganglion cells in the bladder. They regard the condition as analogous to Hirschprung's disease, and, indeed, find the two in association in a few cases. However, it should be noted that while in the bowel disorder there is a complete absence of ganglion cells with a proliferation of nerve fibrils, in the bladder only a diminution in the ganglion cell population was noted. Dr. Leibovitz in our hospital has made very careful and complete counts and found no variation in the number of ganglion cells between normals, obstructed bladders, bladders in Hirschprung's disease and two cases of mega-ureter–megacystis which came to postmortem examination after a full investigation over a number of years. He comments, however, that since there are a large number of ganglion cells in the adventitia at the base of the bladder, which may or may not be stripped, the mode of preparation of specimens has a considerable influence on the count. I am unable to account for Swenson's findings, but I find it hard to believe that an interference with the motor nerve supply would produce a bladder of enlarged functional capacity, capable of holding a huge volume, but capable also of obliterating its lumen. The sensation of fullness is of course impaired in all the very large capacity bladders, and a primary abnormality of the sensory nerves remains a possibility.

In searching for other causes of bladder enlargement we have observed an occasional case in which there is apparently a psychological cause for prolonged holding of urine, but we have been particularly interested in reports by Blotner[4] (1951) and others of large-capacity atonic bladders in untreated diabetes insipidus. Unfortunately, suitable cases have not come our way since we have started accurate cystometric

studies. Ureteric dilatation during the polyuria we have certainly seen, and a similar bladder change seems possible as a result of the high urine flow. It is unlikely that simple renal failure such as occurs in the mega-ureter would ever produce such extreme polyuria as that seen in diabetes insipidus, but there is no doubt that the larger bladders in our series did occur in children with severe polyuria. One wonders if, in the mega-ureter–megacystis syndrome with free reflux, the rapid refilling of the bladder from the ureters after each act of micturition might not produce an effect on the bladder similar to extreme polyuria. If so, then the megacystis might simply be a secondary effect, a consequence of reflux into extremely voluminous ureters–and our search for the primary pathology would be directed to the ureters or the ureteric orifices, rather than to the bladder.

If this were indeed the case, we might expect some difference between the behaviour of the ureter in the mega-ureter–megacystis and the dilated ureter in lower urinary obstruction. We have already noted that, endoscopically, active contractions can be observed at the dilated orifice of the mega-ureters–these are not seen in the obstructed bladders, where often the ureteric orifice retains a normal appearance, unless it is swallowed in a diverticulum. The extraordinary motility of the mega-ureter can also be observed at operation. Others have recorded it by intra-ureteric pressure readings and electro-ureterography. In cineradiological studies, this type of mega-ureter is easy to watch, since reflux fills it with opaque medium introduced into the bladder. Active writhing contractions are the rule; they are usually ineffectual and often reversed. By contrast, where long-standing bladder outlet obstruction has led to reflux, the ureter is immobile, or contracts sluggishly. These facts once again seem to indicate a primary lesion in the ureter in the mega-ureter–megacystis syndrome. Murnaghan[5] (1957) has studied the activity of these ureters in the isolated organ bath and has suggested that there is an abnormality in the arrangement of the muscle layers, resulting in reverse contraction waves and a functional obstruction. Material from the mega-ureter–megacystis cases has, however, not been sufficient to establish this theory on adequate experimental data; for the present it must remain a suggestion.

There is a further condition to be considered, in which a very large-capacity bladder is the rule: it is the syndrome associated with agenesis of the abdominal muscles. In some of the cases there are

multiple anomalies, causing death at or soon after birth; in others prolonged survival is possible, though threatened by progressive renal failure. In 10 cases we have obtained evidence of bladder enlargement in one way or another, though in only three have we had an accurate cystometrogram. Very high figures were recorded, comparable with those for the mega-ureter–megacystis syndrome, although in those with absent abdominal muscles reflux was not usually present, and the figures are therefore true bladder volumes. Once again complete emptying was often obtained, which indicates that we are dealing with a true functional enlargement, rather than an accumulation of residual urine. But several features of the bladder in absent abdominal muscles distinguish it from the megacystis associated with mega-ureter. The trigone is often quite exceptionally large–at cystosocopy the ureteric orifices appear to be out on the lateral bladder wall, and at operation they can easily be brought to the surface of the wound. Moreover, the muscle bundles in the bladder wall have a distinctive appearance: they are smaller and more broken by fibrous tissues than the normal or hypertrophied bladder. Trabeculation has been slight or absent in my cases, and this, together with the very large capacity of the bladder in this syndrome, once more suggests that it is not simply a reaction to the obstruction. Bladder-neck obstruction and urethral valves are often said to be present, but in my series the characteristic finding has been a tapering dilatation of the posterior urethra, somewhat resembling an occasional case of fibro-elastosis but contrasting with the urethral valves.

Enormous ureteric dilatation is characteristic of most cases of absent abdominal muscles, and though it is usual to attribute this to the vesical retention, at least three of my cases had a diaphragmatic obstruction in the lowest half inch of the ureter. One child had the large bladder but no ureteric dilatation–an exceptionally interesting feature; and it seems that if there is a disease in which a "megacystis" is a true congenital anomaly, it is this.

There have been one or two other instances of enormous bladders amongst my cases; one boy undoubtedly had active abdominal muscles, but his abdominal wall had that curious "elephant skin" look, as if the superficial tissues were redundant, and I wondered whether he might have the visceral syndrome but not the fully developed parietal syndrome usually associated with absent abdominal muscles. Another boy of 13 years had bilateral hypoplastic kidneys, very slight ureteric dila-

tation, no reflux and an enormous bladder, which he can empty almost completely. He had extreme polyuria as well as multiple skeletal abnormalities. I cannot pretend to know the cause of his bladder abnormality. He serves to remind us of how various are the congenital deformities of the urinary tract.

Summing up, therefore, the bladder enlargements which we have encountered in children are: First, there is the obstructed bladder with an accumulation of residual urine, very much more common in boys than in girls. The bladder is heavily trabeculated and sacculated and, although distended up to the umbilicus, does not contain an enormous volume of urine. Many forms of congenital obstruction may be responsible; one of these is urethral fibro-elastosis, which simulates bladder-neck obstruction.

Second, we have the megacystis which accompanies bilateral mega-ureter with free reflux: it is a functional enlargement associated with complete contractions. The mega-ureter–megacystis syndrome occurs as often in girls as in boys; it may be suspected clinically by the ability of a child to perform double and triple micturition, producing 120 to 150 ml. on the second and less on the third effort. In contrast to the obstructive cases, the disease is frequently not progressive as long as the urine is kept sterile by chemotherapy and the child is taught a double micturition regime. The occasional case deteriorates; the ureters are too large to be manageable, and there is a grave danger in any operation on such cases. A bladder-neck resection or Y-V plasty is in no way specific, but may reduce the urethral resistance and so diminish the pressure of reflux into the ureters. A plastic reduction of the ureters together with a procedure to prevent reflux may be attempted: Bischoff[6] (1957) in Germany has reported very good results, but my own cases have not done very well. The ureters may be replaced by a loop of ileum, possibly a narrowed loop as suggested by Swenson[7, 8], but when renal failure is already advanced, this is a somewhat hazardous business. Finally, a few cases are fit only for cutaneous ureterostomy.

The third type of bladder enlargement is seen in the "visceral syndrome" associated with absent abdominal muscles. I believe it is not truly obstructive, though there may be obstructive abnormalities in the ureters. Some of the children get on very well without treatment, but we have not yet obtained adequate data on this subject.

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THE CLINICAL SIGNIFICANCE OF SMALL POLYPOID TUMORS OF THE STOMACH*

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ALTHOUGH the word "polyp" should be used with reference only to a gross morphological characteristic of tumors, for most observers it carries a definite histological connotation – that of a benign adenomatous growth. Some controversy has arisen lately with reference to the long accepted hypothesis that gastric adenomas are in some instances precursors of gastric cancer. A policy of observation by radiography and gastroscopy, rather than immediate excision, has been advocated in some clinics, surgery being recommended only for those polyps showing suspicious signs of malignancy – increase in size, ulceration, character of the surface of the polyp and surrounding mucosa, etc. – or giving rise to serious complications such as obstruction or bleeding. The purpose of this study was to determine the degree of accuracy of our present clinical diagnostic means, mainly radiography and endoscopy, in establishing prior to operation the histologic type of small polypoid tumors of the stomach.

Between the years 1947 and 1957 a preoperative diagnosis of gastric polyp was made in 50 patients at Memorial Center. All the patients were operated upon and thus pathological confirmation was obtained in every case. Freedom from symptoms was observed in 24 of the patients, most of whom were first seen at the Strang Cancer Prevention Clinic of the Memorial Center.

Age and Sex. The average age of the group was 54.9 years, with a range of 28 to 69 years. There were 39 women and 11 men.

X-ray Diagnosis. When a single, round, smooth, sessile or pedunculated negative shadow is seen inside the lumen of the stomach during

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TABLE I—PREOPERATIVE DIAGNOSIS: 50 SINGLE "POLYPS"

I. Epithelial	30		
a) Benign		26	
Adenomatous polyp			25
Ectopic pancreas			1
b) Malignant		4	
II. Mesenchymal	13		
a) Benign		11	
Inflammatory polyp			4
Eosinophylic granuloma			2
Leiomyoma			4
Lipoma			1
b) Malignant (leiomyosarcoma)		2	
III. Polyp unclassified	4		
IV. No polyp found at exploration	3		

a gastrointestinal series, the assumption is usually made that it is due to a polyp. At least such a diagnosis is usually a first consideration. When all such lesions are subjected to biopsy, however, we observe that histologic accuracy cannot be expected of the radiologist. Table I shows that, in our experience, only 50 per cent of the lesions proved ultimately to be adenomatous polyps. The other diagnoses are listed in the table. Furthermore, four small adenocarcinomas and two leiomyosarcomas were observed. It is evident then that x-ray studies alone cannot give, with reasonable accuracy, a conclusive diagnosis concerning the histologic nature of a small polypoid tumor of the stomach.

Gastroscopy. In our hands, gastroscopic examination has not shown the same degree of accuracy reported by other investigators. The procedure was performed on 32 patients. In 14, the lesion seen by the radiologist could not be visualized through the gastroscope, although definite pathology was found at laparotomy in 13, of which six were adenomatous polyps, five were benign non-epithelial lesions, one was an adenomatous polyp with malignant transformation, and one was a case of diffuse antral polyposis with cancerous changes. In the remaining case, only enlarged rugal folds were found at surgery. In 14 other cases, polypoid tumors showing no suspicious signs of malignancy to the gastroscopist were described. Of these, seven were adenomatous polyps, four were benign non-epithelial polyps, one was a leiomyosarcoma and

TABLE II—DIAGNOSIS IN ADENOMAS OF THE STOMACH

	Pathological Diag.		
	Adenoma	*Cancer*	*Total*
I. Single Adenomatous Polyp	22	0	22
II. Multiple Adenomatous Polyps	7	4	11
III. Polyposis	9	2	11
IV. Polypoid Carcinoma Arising from Adenoma	0	10	10

one was an unclassified polyp on microscopic examination. In one case no tumor was found at the time of the gastrotomy. A definite suspicion of cancer seemed to be present, according to the endoscopist, in three instances, of which two proved to be benign adenomas, and in the third case a lesion of the stomach could not be found at operation. Finally, there was one case in which the gastroscopic diagnosis was "submucosal neoplasm", which was later shown to be a benign adenomatous polyp at laparotomy.

Small, curable, malignant tumors parading as innocuous benign neoplasms were surgically removed in six patients (12 per cent) because of our policy of submitting all such patients to operation, rather than permitting ourselves the luxury of being guided by clinical impressions. Postoperative mortality did not occur and all have passed the five year period of observation, which is tantamount to cure.

What are the diagnostic and prognostic implications created by the presence of single and multiple adenomatous polyps in the stomach? Table II demonstrates this quite clearly. In none of the 22 cases where a true adenomatous polyp was found at laparotomy and subjected to frozen-section study was carcinoma present. Incidentally, subsequent examination of paraffin sections confirmed the accuracy of the quickly prepared frozen-sections made at the time of laparotomy. Of the 11 instances in which more than one polyp was found at operation and its adenomatous features confirmed, the presence of cancer was established in four. Furthermore, in an additional 11 cases of true polyposis, cancer was present in two. The fact that carcinomatous change had occurred in six of 22 cases (27.3 per cent) in which more than one adenomatous polyp was present in the same stomach indicates the seriousness with

which such a clinical setting must be appreciated. Since Berg[1] has demonstrated quite clearly both benign and carcinomatous changes in the same adenomatous polyp of the stomach, the close relationship of these two tumors cannot be denied. Finally, we observed 10 cases of infiltrating polypoid gastric cancer in which there was positive evidence of a direct association with a benign adenomatous process. Most of these patients died of cancer.

Conclusions

1. The clinical diagnosis of small polypoid tumors of the stomach is misleading and inaccurate.

2. The fallacious management of such lesions by any method short of laparotomy and histologic interpretation of biopsy material is obviously dangerous and unwarranted.

3. The relation between adenomatous polyps and gastric cancer is discussed.

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THE PRESENT DAY MEANING OF INSIGHT*

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Few terms used daily in psychiatry with apparent preunderstood meaning are accompanied by greater vagueness, contradiction and ambiguity than the concept, insight. Although its earliest use is unrecorded, by the beginning of the twentieth century insight had become standardized in psychiatric terminology as "the knowledge on the part of the patient that he is mentally ill". This meaning is still a pertinent one, as in the standard mental status examination, but is amplified by contributions from such diverse fields as philosophy, psychology and conditioned reflex experiments. Further examination of the dynamics and experiences of psychotherapy has emphasized the emotional qualities concerned, and the integrative process involved in its development.

Insight may be described as a series of processes which are fluid and progressive, moving in concentric circles outwards towards an infinite periphery. It differs, however, from the ripples made when a stone is dropped into a pond or a musical note is struck, since there is a living being both causing the original impact and participating in its subsequent course. This more nearly resembles the processes of growth in living things—since insight is formed of living matter and influences the subsequent development of that living matter.

Time relationships are of some significance. As in the examination of the cross-section of an aged tree trunk, a certain incident can later be noted spatially in relation to various internal and external events both preceding and following it. There is often a direct relation between a series of events, in insight development, through influence by earlier ones and an effect exerted on those yet to come. Insight can be altered with the passage of time. Its development is not simply a matter of the instantaneous production of a final state, which remains fixed and unchanged for the remainder of the life of the individual concerned. A previous point of progress may later be sharply localized and seen as an

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important influence on subsequent development, both of itself and of other more remote matters.

It is generally accepted that various facts previously incompletely known, or possibly even apparently unrecognized, can be discovered or more completely illuminated in a purely intellectual fashion. Thus, they can and do become part of the individual's basic store of knowledge. This is essentially a cerebral activity; this is thinking. For purposes of this discussion it can be considered emotion-free.

The dictionary definition of the word insight emphasizes the faculty of *seeing within*. The question arises—a seeing within of what? In the sense in which the term is used in psychiatry it is impossible to name an instance in which insight pertains only to matters purely external to the individual concerned. If there is, and there often may be, a reference at least partly external, it is only to those people or events related to the insight-developing individual in an extremely subjective and personal fashion and, specifically, to that very relationship. In this way insight differs from that body of knowledge of an ordinary nature which we all possess. This difference may, however, be largely a matter of degree since we do show some subjective selectivity and retention of more impersonal facts.

A further point of difference from the ordinary processes of thinking lies in the emotional forces which are part of this very subjectivity. At times these may resemble the ecstatic experience of the mystic; at others, there is the true thrill of discovery. There may often be the problem of surviving the initial shock of some shattering revelation. In still other instances there may be a sense of release and relief, or of mild amusement. Occasionally there is an admixture of various emotions.

Not only must the facts concerned be recognized, but they must be further accepted and incorporated. This requires a continued maintenance of emotional energy and restraint in such balance that the organism can function with awareness and efficiently, in the light of this "new" knowledge. This is a further and long-to-be-continued stage of the process of insight formation. It is neither purely intellectual nor purely emotional but more truly a synthesis of them both. It is here that insight may be directed outward into daily living with the people in the insight-forming individual's immediate milieu.

In the clinical evaluation of insight these various aspects of its development are usually less sharply differentiated. Beginning awareness

may be noted when a patient says, as one did following three interviews for the treatment of severe, functional gastrointestinal symptoms and depression, "I was sitting in church and suddenly I had a clear picture for just a second, of the rut of hate, and nothing but eat, sleep and work I had been in." It is more difficult to give a simple, uncomplicated example of the further progress of insight development except, perhaps, in a detailed account of the successful treatment of nearly any patient.

Although insight begins with expressed awareness—especially of his symptoms, and tends to follow such direct verbal expression, at times the words need not be spoken aloud. It takes form through the patient's expression and recognition of the emotions accompanying such awareness. There is then a continued and continuing process of accepting and assimilating compromises between his wishes and needs and what reality will allow. The possibility of insight development and its final form are influenced by the patient's answer to the unspoken question, "What do you *really* want?"

At the onset of many organic psychoses a varying degree of awareness of real and progressive inadequacies is noted by the patient. The grandiosity of the paretic and the depression of the arteriosclerotic are classically related to such awareness, which may not be recognizable as such by the time he is seen by a physician. In many organic disorders the progress of the disease is so rapid and so severe as to negate and obliterate any continued intellectual awareness whatsoever. A corollary of this is the patient's increasing inaccessibility, which makes him unable to accept any explanation of his difficulties either through his own efforts or through assistance from anyone else.

In the acute toxic psychoses awareness of the illness, as such, by the patient, may vary in degree and from time to time, as much as his awareness of time, person or place. As recovery from the acute physical illness commences, however, such awareness develops, often with feelings of depression or fear because of the previous delirium; or of relief, at being less confused. This is a good example of the obvious fact that the best possible state of physical health is most conducive to intellectual awareness and, hence, to insight development.

Insight may be described variously as partial or absent in the two broad groups of psychoses classified as functional disorders. Such lack of awareness is postulated as a significant difference from the neuroses; in which latter situation, however, the patient is at best only incom-

pletely aware of the deeper significances of his disorder. Where insight appears to be absent, the patient may have fleeting moments of clear, conscious awareness of the unreality of his ideas or the peculiarities of his behavior. This may occur even in long-standing schizophrenic patients, who often appear as inaccessible as those with severe advanced organic brain disease.

It is essential to any description of the paranoid patient that insight is absent. Although he may occasionally admit to minor difficulties, he is completely unable to acknowledge the real facts of what has been happening, the possibility of an error in his interpretation of such facts or that certain incidents might occur coincidentally rather than causally. Such major inability usually precludes any deeper self-exploration. Reality can offer such a patient little which is so glamorous, so assuring or satisfying as the world of his delusions.

In a patient with the schizophrenic disorders considered "acute", "turmoil" or catatonic, careful history will often show that psychotic symptoms are preceded by a spontaneous recognition by the patient that something is amiss and that this is *within* himself. Usually, by the time he is seen by a psychiatrist, however, such a conscious awareness of his difficulties has largely vanished, to be expressed only in more symbolic form. At the same time, material from hitherto unrecognized deep conflicts may be more or less evident in his speech and behavior, often without the emotional accompaniment usually seen with such material. As he begins to recover, the patient recognizes more clearly that something *was* (and *is*) wrong within himself. The material of his underlying conflicts is perhaps less evident to the observer, but is now accompanied by a fuller and more overt emotional expression. Eventually, a clear awareness of the symptoms at the height of his illness may be "forgotten", and the emotional forces unleashed at that time may have largely subsided. Synthesis is now slowly taking shape.

In those instances of illness in response to emotional trauma, such as "combat fatigue" with elements of both catatonic and conversion symptoms, insight formation may commence suddenly and dramatically through various external means which help the patient to re-live actively the previous traumatic situation and discharge thereby, suddenly and more completely, the emotional forces associated with it. Perhaps such sudden development occurs because the precipitating incident was itself so dramatic and so sudden. Even here, however, it is necessary

to permit an opportunity for gradual synthesis over a more prolonged period than was involved in the birth of insight, although usually a shorter time than in similar reactions not precipitated by such trauma.

In the mood disorders, a clear recognition by the patient that "something is wrong" is much nearer the surface. In hypomanic states, this is without his full recognition of the extent of the change and with no more apparent concern with it than over minor physical difficulties. Severely depressed patients are generally quite aware of the nature and severity of their symptoms even if unable to put this awareness into words. Depressions of a milder nature are often not recognized as such by the patient and are often considered mere manifestations of a physical disorder. Mood disturbances are frequently related causally to some external event not only by the patient and his relatives but by physicians as well. Rarely the patient may speak spontaneously of an apparently contradictory relationship between an external event and his own feelings, e.g., the death of a loved one, with an elation; marriage or "wanted" childbirth, with a depression. In our present state of clinical knowledge, no one can completely understand or explain many mood disturbances. Most patients with this condition attain a fairly clear awareness of the prodromal symptoms and of the possible course of an episode. The psychiatrist can be of particular aid to a cyclothymic patient by increasing his knowledge of such symptoms to help him so modify his life in their possible recurrence that serious disturbances can be better controlled early and with less disastrous consequences.

In conclusion, brief mention may be made of insight in the therapist. This implies an inner knowledge of himself which is both used within himself and so incorporated into his personality that it can be directed outward to become part of his daily living. His knowledge of other human beings and his skill in the treatment of their illness is an insight to be accepted as a responsibility and to be used with true humility. He judges the nature and severity of the patient's symptoms on the basis of his medical knowledge and experience. He stands as the steadfast rock against which the turbulent emotions of the patient may beat; accepting the various roles assigned him from the complex drama of the patient's life, responding, however, not in kind, but with continued patient understanding. He serves as example and positive preceptor in the synthesis of daily living, and thereby helps the patient find what he, the patient, really wants.

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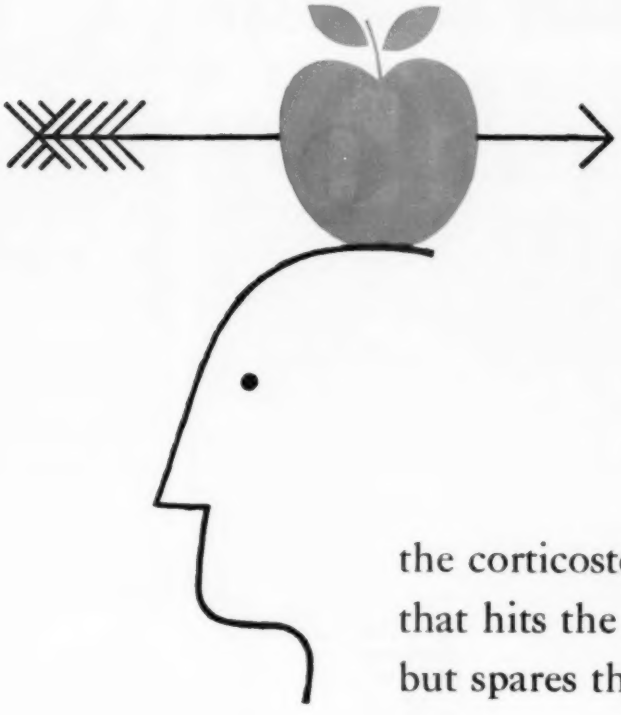

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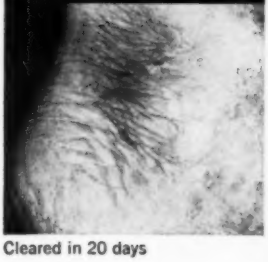

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References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.; Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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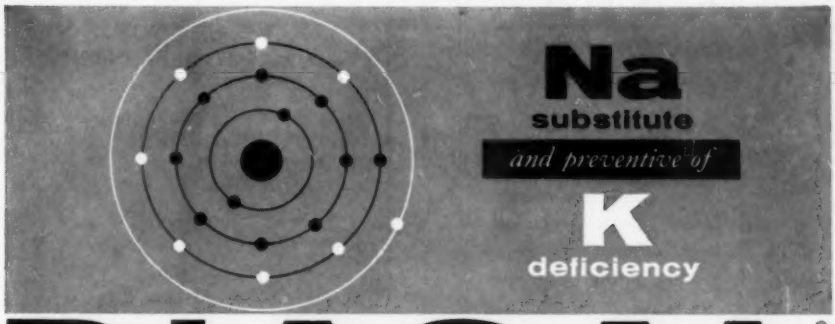

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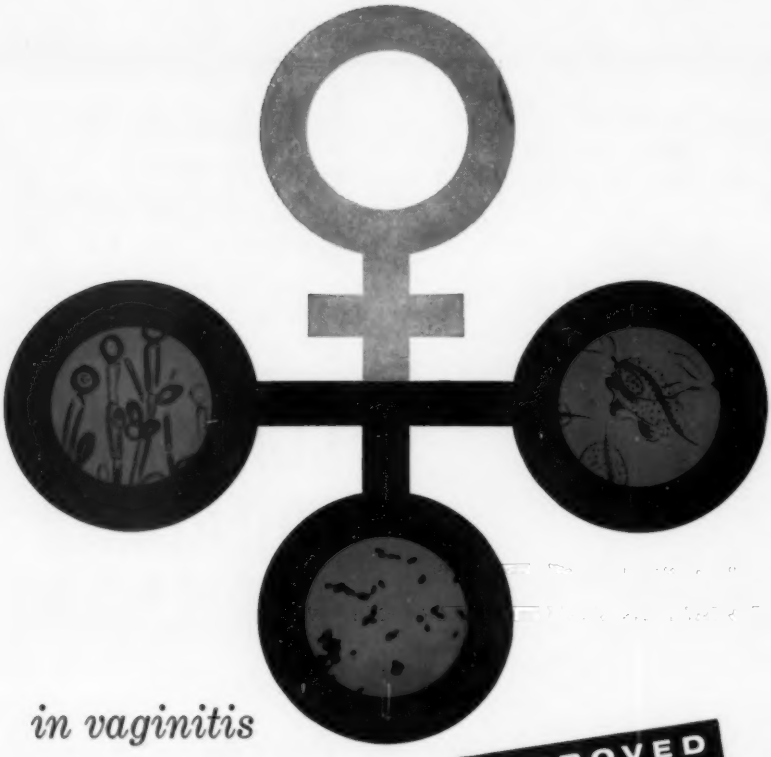

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